EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 09/567,451	Confirmation No.	: 5428
First Named Inventor	: Kenneth ALBERT		
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Examiner	: Susan Tran		
Docket No.	: 100338.55781US		
Customer No.	: 23911		
Title	: Chronotherapeutic Diltiazem Formulations and the Administration Thereof		

AMENDMENT

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The following amendments and remarks are presented in response to the Office Action mailed September 2, 2005.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 31 of this paper.

Amendments to the Claims:

The listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims

1. (Currently amended): An orally administrable controlled-release composition comprising a pharmaceutically acceptable form of diltiazem selected from the group consisting of diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours the dosage comprising at least one bead comprising a core and at least one coating, the at least one bead being formulated in an oral dosage form containing from about 120 mg to about 540 mg of the form of diltiazem, the diltiazem in the core of each bead associated with excipients, the at least one coating covering the core comprising an amount of a water swellable and diffusible coating which permits hydration of the core by gastrointestinal fluids, the water swellable and diffusible coating comprising the following constituents:. (i) an amount of at least one lubricant and/or an amount at least one hydrophilic polymer and. (ii) further comprising as an essential constituent an amount at least one water insoluble swellable neutral copolymer, wherein said constituents. (i) and. (ii) which comprise said coating, the ratios thereof, and the amount of said coating are formulated such that said orally administrable composition: A) in vitro exhibits the following in vitro release characteristics;

(i) releases the diltiazem or a pharmaceutically acceptable salt thereof into a aqueous medium at the following rates when measured using the method of United States Pharmacopoieia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after about 2 hours;

(b) between about 7% and about 35% after about 4 hours;

(c) between about 30% and about 58% after about 8 hours;

(d) between about 55% and about 80% after about 14 hours;

(e) in excess of about 75% after about 24 hours;

and/or. (ii) releases the diltiazem or pharmaceutically acceptable salt thereof into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;

(c) between about 30% and about 68% after about 8 hours;

(de) in excess of about 75% after about 24 hours;

and

further wherein said orally administrable composition having said in vitro release characteristics results in a composition that:

B) when orally given to humans exhibits the following properties:

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with or without food according to the same FDA guidelines or criteria;

and

(iii) provides a Cmax of diltiazem in the blood at between about 10 hours and 15 hours after administration.

2. (Currently amended): The controlled release preparation of claim 1 wherein the water insoluble swellable neutral copolymer is selected from the group consisting of

(i) a water-, acid-, and base-insoluble polymer of a neutral acrylic polymer,

(ii) a neutral acrylic copolymer of ethyl acrylate and methyl methacrylate, and

(iii) a neutral copolymer without any functional groups that form water insoluble films and the lubricant is selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative and/or the hydrophilic polymer is selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof.

3. (deleted)

4. (deleted)

5. (Currently amended): The controlled-release preparation of claim 1 in which the form of diltiazem is adapted to be control released after administration of the preparation over a period of time and is more preferably adapted to release the diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after about 2 hours;

(b) between about 16% and about 21% after about 4 hours;

(c) between about 44% and about 62% after about 8 hours;

(d) between about 69% and about 76% after about 14 hours; and

(e) and in excess of about 85% after about 24 hours;

and/or. (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after about 2 hours;

(b) between about 16% and about 30% after about 4 hours;

(c) between about 44% and about 62% after about 8 hours;

(d) in excess of about 80% after about 24 hours.

6. (Previously amended): The preparation of claim 4 wherein the Cmax of diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

7. (Previously amended): The preparation of claim 1, 2, 5 or 6 wherein the form of diltiazem is Diltiazem HCl.

8. (Previously amended): The preparation of claim 6 wherein the preparation is a diffusion controlled preparation.

9. (previously amended): The preparation of claim 5 wherein the preparation releases the diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

10. (previously amended): The preparation of claim 9 in capsule form.

11. (previously amended): The preparation of claim 9 in tablet form.

12. (previously amended): The preparation of claim 9 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

13. (original): The preparation of claim 12 wherein the diltiazem is mixed. (in whole or in part) with the wetting agent.

14. (previously amended): The preparation of claim 13 wherein the wetting agent assists to maintain the solubility of the diltiazem in each microgranule, ensuring that the solubility of the diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

15. (previously amended): The preparation of claim 14 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

16. (previously amended): The preparation of claim 12 wherein the preparation comprises a mixture of the diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer

of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

17. (previously amended): The preparation of claim 16 wherein the membrane comprises a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.

18. (previously amended): The preparation of claim 17 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane. (high concentration inside and low concentration outside).

19. (previously amended): The preparation of claim 13 wherein the diltiazem is mixed with the wetting agent and the membrane comprises an acrylic membrane and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

20. (previously amended): The preparation of claim 9 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent. (other than a wetting agent) to assist in the release of the diltiazem from the preparation.

21. (previously amended): The preparation of claim 20 wherein the dissolution agent is an organic acid comprising adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid or tartaric acid which permits the diltiazem to dissolve in gastrointestinal fluids even when the microgranules pass into the regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

22. (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 1 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning, the method comprising administering to a patient in need thereof the preparation in the evening.

23. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 2 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

24. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 5 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

25. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 6 to the

patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

26. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 7 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

27. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 8 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

28. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 9 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

29. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 10 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

30. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 11 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

31. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 12 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

32. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 13 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

33. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 14 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

34. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 15 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

35. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 16 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

36. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 17 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

37. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 18 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

38. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 19 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

39. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 20 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

40. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 21 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

41. (currently amended): The preparation of claim 1 wherein the preparation contains 120 mg of diltiazem.

42. (currently amended): The preparation of claim 1 wherein the preparation contains 180 mg of diltiazem.

43. (currently amended): The preparation of claim 1 wherein the preparation contains 240 mg of diltiazem.

44. (currently amended): The preparation of claim 1 wherein the preparation contains 300 mg of diltiazem.

45. (currently amended): The preparation of claim 1 wherein the preparation contains 360 mg of diltiazem.

46. (currently amended): The preparation of claim 1 wherein the preparation contains 420 mg of diltiazem.

47. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 41, 42, 43, 44, 45 or 46 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

48. (previously amended): The preparation of claim 17 wherein the wetting agent is selected from:

sugars;
saccharose, mannitol, sorbitol;
lecithins;

C_{12} to C_{20} fatty acid esters of saccarose;
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene;
sorbitan fatty acid ester;
polyglycides-glycerides and polyglycides-alcohols esters
Metal salts.

49. (currently amended): The preparation of claim 12 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer selected from the group consisting of hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which enables the bead to be hydrated by the introduction of gastrointestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

50. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 48 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

51. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 49 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

52. (currently amended): A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to 1 which comprises the following constituents:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	(Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide. (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP. (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0. (used for mixing)

53. (currently amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 52 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

54. (previously amended): The preparation of claim 12 in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85%. (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent. (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 5% and about 20%. (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

55. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 54 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

56. (previously amended): The preparation of claim 12 in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73%. (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent. (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 7% and about 11%. (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

57. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 56 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

58. (previously amended): The preparation of claim 12 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of diltiazem during the tablet process, together with suitable excipients and adjuvants.

59. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 58 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

60. (previously amended): The controlled-release preparation of claim 2 in which the diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85%. (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent. (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 5% and about 20%. (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

61. (original): The preparation of claim 60 wherein the microgranules are in capsule form.

62. (original): The preparation of claim 60 wherein the microgranules are in tablet form.

63. (previously amended): The preparation of claim 60 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73%. (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent. (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 7% and about 11%. (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

64. (currently amended): A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to Claim 1, which preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85%. (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent. (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20%. (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants,

wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	(Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide. (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP. (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0. (used for mixing).

65. (previously amended): The preparation of claim 60 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the

microgranules of diltiazem during the tablet process, together with suitable excipients and adjuvants.

66. (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 60 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

67-109. (cancelled)

110. (currently amended): A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to Claim 1, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the wetting agent is selected from:

sugars;
saccharose, mannitol, sorbitol;
lecithins;
C_{12} to C_{20} fatty acid esters of saccarose;
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene;
sorbitan fatty acid esters;
polyglycides-glycerides and polyglycides-alcohols esters
Metal salts.

111. (cancelled)

112. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 110 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

113. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 111 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

114. (currently amended): A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to Claim 4

wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	(Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0

(g)	Titanium dioxide. (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP. (dry of 30%)	0.01 - 0.015
(k)	neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0. (used for mixing)

115. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 112 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

116. (currently amended): A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to Claim 5 , wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85%. (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent. (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants which permits hydration of the core by gastrointestinal fluids.

117. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 116 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

118. (currently amended): A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to Claim 5 , wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73%. (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent. (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 7% and about 11%. (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants which permits hydration of the core by gastrointestinal fluids.

119. (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 118 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

120-121. (cancelled)

122. (currently amended): A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to Claim 1 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85%. (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent. (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 5% and about 20%. (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants which permits hydration of the core by gastrointestinal fluids.

123. (original): The preparation of claim 122 wherein the microgranules are in capsule form.

124. (original): The preparation of claim 122 wherein the microgranules are in tablet form.

125. (previously amended): The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73%. (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent. (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethyl-cellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 7% and about 11%. (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

126. (previously amended): The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	(Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide. (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP. (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester. (dry of 30%)	7 - 11
	Purified water USP	0. (used for mixing).

127. (previously amended): The preparation of claim 122 or 124 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of diltiazem during the tablet process, together with suitable excipients and adjuvants.

128. (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 122, 123 or 124 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

129. (previously presented): The preparation of claim 110 wherein the neutral copolymer is selected from the group consisting of

(i) a water-, acid-, and base-insoluble polymer of a neutral acrylic polymer;

(ii) a neutral acrylic copolymer of ethyl acrylate and methyl methacrylate;

(iii) a neutral copolymer without any functional groups that form water insoluble films; and

the lubricant is selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative and/or the hydrophilic polymer is selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof.

130. (previously presented): The preparation of claim 116, 118 and 122 wherein the lubricant is selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative.

131. (previously presented): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 129 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

132. (previously presented): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 130 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

133. (Previously presented): The preparation of Claim 1 in capsule form.

134. (Previously presented): The preparation of Claim 1 in tablet form.

135. (Previously presented): The preparation of Claim 2 in capsule form.

136. (Previously presented): The preparation of Claim 2 in tablet form.

REMARKS

Entry of the foregoing amendments and reconsideration of the subject application, as amended, and in light of the remarks which follow are respectfully requested. By the present amendments the claims are amended to cure obvious informalities noted by the Examiner and to obviate a rejection made under §112 first paragraph, written description and a §112 second paragraph rejection.

At the outset Examiner Tran and Examiner Hartley are both thanked for the helpful personal interview held in December 1, 2005 with the undersigned and Dr. Salim Mamajiwalla, Patent Agent, and representative of Biovail Corporation, the Assignee of the subject application.

During the interview, all of the outstanding rejections were discussed in detail. The §112 written description rejection was discussed. The undersigned indicated that the claims would be amended to insert "about" without prejudice to the previous claim phrasecology which Applicants still respectfully maintain finds written description support from the as-filed specification and the recited dissolution ranges which explicitly encompasses the recited values.

The formal issues were addressed. It was noted that the noted informalities would be cured by amendment.

The double patenting rejection was discussed. Applicants' representative noted that this rejection is moot in view of the abandonment of the earlier related application in favor of the instant application.

The prior art rejections including the newly applied prior art were discussed. It was emphasized that none of the prior art teaches a chronotherapeutic diltiazem formulation as claimed nor do any teach of the references a diltiazem formulation that would inherently possess the desired properties of a chronotherapeutic diltiazem formulation as recited in the claims pending herein. Particularly, all of the cited prior art relating to diltiazem formulations possess T_{max} times (the time at which diltiazem levels in the serum (C_{max}) are at their highest) which occurs about 6 hours after administration. By contrast, the T_{max} for the chronotherapeutic diltiazem formulation of the invention is attained about 10-15 hours after administration.

As explained in the as-filed specification, and in the substantial declaration evidence already of record, especially the Mathiowitz Affidavit, this substantial difference in T_{max} (4-9 hour difference) is greatly advantageous because the subject formulations (preferably administered in the evening) provide for diltiazem levels in the serum to peak in the early morning and waking hours, statistically the time period when the risk of heart attack and stroke are at their highest. Thereby, the present invention provides an improved extended release (once-daily) diltiazem formulation which should alleviate or reduce the risk of heart

attack or stroke compared to previous diltiazem formulations, especially those possessing T_{max} values as recited in the prior art of record.

Further, it was respectfully argued that the cited prior art does not provide the requisite motivation to modify their formulations to arrive at a diltiazem formulations possessing the dissolution and pharmacokinetic properties of the present invention, especially a T_{max} between 10-15 hours after administration.

In fact, it was noted that none of the cited prior art even mentioned any chronotherapeutic diltiazem composition much less the intrinsic advantages thereof. Based thereon, Applicants argued that the prior art alone or in combination did not fairly teach or suggest the modification of the control release coatings used in the prior art diltiazem formulations in order to obtain a chronotherapeutic diltiazem formulation as claimed herein. Moreover, Applicants further argued that the prior art, even assuming that it provided the requisite motivation [to produce a chronotherapeutic diltiazem formulation] also does not provide an expectation of success, namely that the mere modification of the control release coating would both (i) allow for therapeutic levels of diltiazem to be released from the formulation and to be present in the serum over the 24 hour dosage and (ii) to provide for T_{max} to be attained substantially after administration, i.e., 10-15 hours after administration when the risk of stroke and heart attack are the greatest. Also, it was noted that the proposed additional comparison would be improper since it would essentially "compare the invention to itself".

Based on the foregoing arguments, the Examiners seemed to appreciate the significant differences between the invention vis-a-vis the prior art, especially the recited dissolution and release rates, as well as T_{max} and C_{max} occurring 10-15 hours after administration. The Interview Summary record is consistent with Applicant's understanding of the substance of the interview.

Turning now to the Office Action [non-final rejection dated September 2, 2005], Claims 1-2, 5-66, 112-119 and 122-136 stand provisionally rejected based on obviousness-type double patenting grounds based on the claims of related commonly assigned United States Patent Application No. 09/465,338. This rejection is moot as the '338 Application has been abandoned in favor of the present patent application Withdrawal of this rejection is therefore respectfully requested.

Claims 1-2, 5-66, 110, 112-119, and 122-136 further stand rejected under 35 USC §112 first paragraph as allegedly not finding appropriate written description support from the as-filed specification. Essentially, the Examiner maintains that the recited dissolution time periods improperly introduce new matter into the claims since they recite "exact" times rather than modifying these times with the word "about" as in the patent application. This rejection is respectfully traversed, however, Applicants note that the present claim amendments adopt the Examiner's proposed claim phraseology.

In particular, Applicants maintain that the recited dissolution ranges necessarily and explicitly included all of the dissolution times recited in the claims under rejection.

Therefore, Applicants respectfully maintain that the claims as previously amended do not introduce any subject matter not finding literal support from the as-filed specification. However, in order to expedite prosecution (as noted a commercial product corresponding to the claimed chronotherapeutic diltiazem formulation is currently being sold by the subject Assignee) the claims have been amended in order to render this rejection moot.

Also, Claim 1 stands rejected based on 35 USC §112 second paragraph as allegedly being indefinite. This rejection is believed to be moot as claim 1 has been amended to provide antecedent basis for the "amounts" of coating constituents and the coating.

Claims 1-2, 5-51, 53-63, 65-66, 110, 113, 115-119 and 122-136 also stand rejected under 35 USC §103 based on Geoghegan et al, EP 0 856 313. This rejection is respectfully traversed for the same reasons presented at the interview and contained in Applicants' previous response and the Affidavit by Dr. Edith Mathiowitz. Essentially, as substantiated by the comparative evidence already of record, Geoghegan does not teach or suggest a chronotherapeutic diltiazem formulation as claimed. Rather while Geoghegan admittedly teaches a controlled release diltiazem formulation comprising a diltiazem immediate release core surrounded by multilayer controlled release membrane comprising a water insoluble and water insoluble polymer, and which possesses specific release rates over the 24 hour dosage period (which overlap with the present claims), Geoghegan completely fails to teach or suggest a diltiazem formulation which attains C_{max} at a time between 10-15 hours after administration. Rather, as substantiated by comparative evidence already of record and

extensively discussed in the Mathiowitz Affidavit, Geoghegan instead describes controlled release diltiazem formulations which attain C_{max} about 6 hours after administration. (See especially para. 22 of the Mathiowitz Affidavit).

As explained at the interview, Geoghegan completely fails to teach or suggest the modification of their disclosed controlled release coatings in order to obtain a chronotherapeutic diltiazem formulation as claimed herein. (As previously argued the control release coating lacks an uncharged copolymer that provides for pH-independent drug release, rather all the co-polymers exemplified by EP 313 are charged co-polymers.)

In fact the reference does not even contain the word chronotherapeutic in its "four corners". Nor does the reference provide any basis for modifying the disclosed diltiazem formulations to produce a diltiazem formulation which attains C_{max} between 10-15 hours after administration. Indeed the reference does not speak to any disadvantageous properties of their disclosed diltiazem formulations which would motivate substantial modification. (As discussed in the Mathiowitz Affidavit and the in vivo studies discussed therein the change of C_{max} from 6 hours to 10-15 hours is a very substantial change having pronounced effects on therapeutic efficacy, especially the avoidance of heart attacks and stroke in users of the subject chronotherapeutic composition).

Also, there is nothing in the reference which would enable the skilled artisan to reasonably infer that the release coatings of Geoghegan, even if modified to e.g., include an uncharged co-polymer, would result in a controlled release diltiazem possessing the desired

C_{max} between 10-15 hours after administration and which still releases the desired therapeutic diltiazem levels over the 24 hour period. As explained by Dr. Mathiowitz this is not a trivial exercise, rather the design of the subject chronotherapeutic formulation required careful balancing of the various constituents which comprise the diltiazem formulation, especially in the control release coating and there was no assurance that such modification would have been successful. For example, it was entirely possible that the core might need to be modified as well or alternatively to the controlled release membrane layers. The mere generic suggestion to manipulate the formulation as suggested in the Office Action is insufficient motivation especially given the enhanced results attained by the subject invention.

Therefore, Applicants respectfully maintain that the Geoghegan reference does nor provide any motivation to modify their teachings in order to arrive at a chronotherapeutic diltiazem formulation possessing the advantageous combination of properties required by the subject claims, especially that C_{max} is attained 10-15 hours after administration. Therefore, Applicants respectfully submit that the §103 rejection of Claims 1-2, 5-51, 53-63, 65, 6, 110, 112-113, 115-119 and 122 -136 should be withdrawn as it is based on improper hindsight the reference containing no mention of a chronotherapeutic diltiazem formulation.

Claims 1-2, 5-51, 53-63, 65-66, 110, 112-113, 115-119 and 122-136 further stand rejected under 35 USC §103 based on Deboeck et al. (WO 93/00093). This rejection was

also discussed extensively at the interview. Applicants' patentability arguments are substantially similar as the arguments made over Geoghegan.

Again, while Deboeck teaches a controlled release diltiazem formulation that has somewhat overlapping *in vitro* dissolution ranges over a 24 hour period to the claimed diltiazem formulation, Deboeck also fails to teach or suggest a chronotherapeutic controlled release diltiazem formulation as claimed wherein the blood serum level of diltiazem peak 10-15 hours after administration. Rather as established by comparative evidence already of record a commercially available diltiazem formulation according to WO'093 (Tiazec) attains C_{max} only 6 hours after administration, consistent with Geoghegan . Indeed as with Geoghegan, the Deboeck patent reference does not even mention a chronotherapeutic diltiazem formulation. Nor does the reference provide any motivation to substantially modify the pharmacokinetic properties of their disclosed controlled release composition in order to substantially change the time that C_{max} is attained relative to administration. As noted, a diltiazem composition which has a T_{max} of only 6 hours possesses very different PK properties than a diltiazem formulation with a T_{max} of 10-15 hours, and moreover is superior therapeutically as it should prevent stroke and heart attack in more users than the Deboeck formulation or another similar non-chronotherapeutic diltiazem formulation. (For clinical support of this argument see *in vivo* study discussed in paragraphs 37-38 and Exhibit 12 of the Mathiowitz Affidavit.).

Claims 1-2, 5-51, 53-63, 65-66, 110, 112, 113, 115-19, and 122-136 further stand newly rejected under 35 USC §103 based on Hendrickson et al. (US Patent No. 5,286,497) in view of Barry et al. (US Patent No. 5,055,306) This rejection is also respectfully traversed for substantially the same reasons as the previously discussed §103 rejections.

As discussed at the recent personal interview, Hendrickson likewise fails to teach or suggest a chronotherapeutic controlled release diltiazem formulation having the specific combination of properties of the present invention. Rather while Hendrickson purports to teach another once-a-day diltiazem formulation , the dissolution release rates and the T_{max} are substantially different than those of the present invention. Indeed upon review of Table X, it is apparent that the Hendrickson once-a-day diltiazem composition attains C_{max} at 6 hours after administration. By contrast, the present chronotherapeutic diltiazem formulation attains C_{max} between 10-15 hours after administration. Thus, all of the prior art diltiazem formulations are consistent in the fact they attain C_{max} about 6 hours after administration. Also, none mention a chronotherapeutic diltiazem formulation as claimed. This substantiates Applicants' argument as it bolsters the argument that the state of the prior art in once-a-day diltiazem formulations teaches away from the claimed invention.

The Examiner acknowledges the deficiency of Hendrickson but urges that it would have been obvious to modify the Hendrickson formulation by incorporating the neutral co-polymer containing coating used in Barry since both references teach the advantages of delayed release granules and coatings. This rejection is vigorously traversed.

Neither the Hendrickson nor the Barry reference provides any incentive to produce a chronotherapeutic diltiazem possessing the specific release properties over time as the subject chronotherapeutic diltiazem formulation. Therefore, the rejection is respectfully submitted to rely on improper hindsight as there is no basis absent Applicants' invention to combine the teachings of the references. Moreover, even assuming for the sake of argument that the references were properly combined, the references alone or in combination would not motivate a skilled artisan to vary the polymeric constituents, amounts thereof, and amount of the release coating in order to arrive at a controlled release diltiazem formulation possessing the specific release properties and in particular attaining C_{max} only after 10-15 hours after administration.

Therefore, Applicants respectfully submit that the prior art rejection of claims 1-2, 5-51, 53-63, 65, 66, 110, 112, 113, 115-119 and 122-136 based on Hendrickson et al in view of Barry et al should be withdrawn as the references are improperly combined and even when combined do not teach or suggest the claimed once-a-day chronotherapeutic diltiazem formulation.

Based on the foregoing this application is believed to be in condition for allowance. A notice to that effect is respectfully solicited.

Also, given the great commercial importance of this application, especially given that a corresponding product has been FDA approved and is on the market, if any issues remain outstanding after consideration of this Response it would be greatly appreciated if the

Examiner would telephone the undersigned to see if such issues may be resolved without the need for an additional Office Action.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 04-1679 (Docket #100338.55781US).

Respectfully submitted,

January 3, 2006

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(54) Controlled absorption diltiazem formulations

(57) A controlled absorption diltiazem pellet formulation for oral administration comprises a core of diltiazem or a pharmaceutically acceptable salt thereof in association with an organic acid, and a multi-layer membrane surrounding the core and containing a major proportion of a pharmaceutically acceptable film-forming, water insoluble synthetic polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble synthetic polymer. The number of layers in the membrane and the ratio of the water soluble to water insoluble polymer, when said water soluble polymer is present, being effective to permit release of diltiazem from the pellet at a rate allowing controlled absorption thereof over not less than a twelve hour period following oral administration. The pellet has a dissolution rate in vitro which when measured in a dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 results in not more than 35% of the total diltiazem being released after 2 hours of measurement. Not more than 60% of the total diltiazem is released after four hours of measurement and 100% of the diltiazem is released no earlier than after 8 hours of measurement in said apparatus.

EP 0 856 313 A1

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Description

This invention relates to controlled absorption pharmaceutical formulations and, in particular, to controlled absorption forms of diltiazem for oral administration.

Diltiazem-cis-(+)-3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one, is a benzothiazine derivative possessing calcium antagonist activity. Diltiazem blocks the influx of calcium ions in smooth and cardiac muscle and thus exerts potent cardio-vascular effects. Diltiazem has been shown to be useful in alleviating symptoms of chronic heart disease, particularly angina pectoris and myocardial ischemia and hypertension, while displaying a low incidence of side effects. Diltiazem is conventionally administered in tablet form (30 mg or 60 mg) as diltiazem hydrochloride sold under the Trade Mark Cardizem (Marion Laboratories Inc.). Diltiazem in tablet form (30 mg) is also sold under the Trade Mark Herbesser (Tanabe Seiyaku). Diltiazem is also sold in capsule form.

Conventional diltiazem therapy starts with 30 mg administered 4 times daily. The dosage is gradually increased to 240 mg, given in divided doses three or four times daily, at one- to two- day intervals until an optimum response is obtained. Diltiazem is extensively metabolized by the liver and excreted by the kidneys in bile. According to professional use information issued by Marion Laboratories Inc., Cardizem is absorbed from the known tablet formulation to about 80% and is subject to an extensive first-pass effect, giving an absolute bioavailability, compared to intravenous administration, of about 40%. Single oral doses of 30 to 120 mg of Cardizem result in peak plasma levels 2-3 hours after administration. Detectable plasma levels occur within 30-60 minutes after administration indicating that Cardizem is readily absorbed.

The plasma elimination half-life following single or multiple administration is approximately 3-5 hours. Therapeutic blood levels of Cardizem are thought to be in the range of 50-200 ng/ml.

As stated above, conventional diltiazem capsules and tablets are administered three or four times daily. Such frequent drug administration may reduce patient compliance and produces irregular blood levels; thus adverse therapeutic effects can arise.

An article by McAuley, Bruce J. and Schroeder, John S. In Pharmacotherapy 2: 121, 1982 states that peak plasma levels of diltiazem occur within one hour with normal capsules and within 3 to 4 hours with sustained release tablets. However, the Applicants have found that peak plasma levels of diltiazem occurring within 3 to 4 hours following administration were incompatible with effective and efficacious twice-daily administration of diltiazem, and that peak plasma levels occurring within 6 to 9 hours as obtained in the case of the controlled absorption diltiazem formulation of the Applicants' EP-A-0 149 920 satisfy accepted criteria for twice-daily administration of diltiazem, with preferred levels occurring within 8 to 9 hours. Furthermore, it will be appreciated peak plasma levels of diltiazem occurring within 3 to 4 hours are incompatible with effective and efficacious once-daily administration of diltiazem.

The Applicants' EP-A-0 149 920 describes and claims an effective diltiazem formulation for twice-daily administration. The formulation is distinguished by a characteristic dissolution rate when tested under specified conditions, not least its controlled absorption characteristics in vivo, which offer distinct advantages over existing formulations. However, it has been found with certain formulations prepared in accordance with EP-A-0 149 920, when manufactured in production batches commensurate with commercial scale manufacture to the indicated specifications, that the in vitro performance of the formulation disimproved beyond acceptable limits when stored over the normally required shelf-life periods. This was found to be particularly the case with formulations containing the naturally occurring polymer shellac. It is known that such naturally occurring polymers can exhibit considerable variability in quantity and quality depending on the source and time of collection and accordingly there remains a need to produce alternative formulations which do not require their use.

It is an object of the present invention to provide a controlled absorption diltiazem formulation suitable for administration no more frequently on the average than at twelve hour intervals.

It is another object of the present invention to provide a controlled absorption diltiazem formulation suitable for once-daily administration and which is bioequivalent to known oral formulations of diltiazem.

It is another object of the present invention to provide a controlled absorption diltiazem formulation suitable for once- and twice-daily administration, which is bioequivalent to known oral formulations of diltiazem, which has good stability over normal shelf-life periods of eighteen months to two years, and which contains only synthetic polymeric materials.

A further object of the present invention is to improve the method of manufacture of said formulations.

Another object of the present invention is to provide a controlled absorption diltiazem formulation which is particularly effective when administered at specific times during the day.

Accordingly, the invention provides a controlled absorption diltiazem pellet formulation for oral administration, said pellet comprising a core of diltiazem or a pharmaceutically acceptable salt thereof in association with an organic acid, the diltiazem component and the organic acid being present in a ratio of from 50:1 to 1:1, and a multi-layer membrane surrounding said core and containing a major proportion of a pharmaceutically acceptable film-forming, water insoluble synthetic polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble syn-

thetic polymer, the number of layers in said membrane and the ratio of said water soluble to water insoluble polymer, when said water soluble polymer is present, being effective to permit release of said diltiazem from said pellet at a rate allowing controlled absorption thereof over, on the average, not less than a twelve hour period following oral administration, said rate being measured in vitro as a dissolution rate of said pellet, which when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 substantially corresponds to the following dissolution pattern:

a) no more than 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) no more than 60% of the total diltiazem is released after 4 hours of measurement in said apparatus; and
c) 100% of the diltiazem is released no earlier than after 8 hours of measurement in said apparatus.

It will be appreciated that, when a once-daily formulation of the present invention is given prior to bedtime, it may be desirable to administer a formulation having a slower initial release during the night followed by an increased rate of release occurring in the morning as the patient awakens and commences activity.

Therefore, it may be desirable to administer a formulation which is effective for once-daily administration wherein the in vitro dissolution rate has the following pattern:

a) from 0 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 0 to 45% of the total diltiazem is released after 4 hours of measurement in said apparatus;
c) from 10 to 75% of the total diltiazem is released after 8 hours of measurement in said apparatus;
d) from 25% to 95% of the total diltiazem is released after 13 hours of measurement in said apparatus; and
e) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

It will also be appreciated that the active ingredients of the present invention are generally given to chronically ill patients wherein a steady state equilibrium is reached after several days or so of treatment. Patients that have achieved steady state are less susceptible to fluctuations ordinarily observed following administration of a single dose.

Those skilled in the art will appreciate that depending on the time of administration throughout the day and the preferred bioprofile to be achieved, products may be formulated with dissolution profiles falling within various subdivisions within the foregoing ranges. A particularly preferred once-daily product normally to be administered prior to bedtime or in the morning upon awakening would be formulated to achieve the following dissolution profile:

a) from 0 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 5 to 45% of the total diltiazem is released after 4 hours of measurement in said apparatus;
c) from 30 to 75% of the total diltiazem is released after 8 hours of measurement in said apparatus;
d) from 60 to 95% of the total diltiazem is released after 13 hours of measurement in said apparatus; and
e) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

The time of administration discussed above for once-daily administration of drugs is also applicable to twice-daily formulations. Those skilled in the art will appreciate that twice-daily products may be formulated within selected subdivisions depending on the preferred time of administration.

The invention thus further provides a diltiazem pellet formulation according to the above which is effective for twice-daily administration wherein the in vitro dissolution rate has the following pattern:

a) from 5 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 35 to 85% of the total diltiazem is released after 6 hours of measurement in said apparatus; and
c) 100% of the total diltiazem is released no earlier than after 8 hours of measurement in said apparatus.

A particularly preferred diltiazem formulation which is effective for twice-daily administration is one wherein the in vitro dissolution rate has the following pattern:

a) from 5 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 55 to 80% of the total diltiazem is released after 6 hours of measurement in said apparatus; and
c) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

Whereas the formulation of EP-A-0 149 920 is eminently suitable for twice-daily administration of diltiazem, the Applicants have found in the case of the present invention that peak plasma levels of 10 to 19 hours are essential in satisfying accepted criteria for once-daily administration of diltiazem, with preferred levels occurring within 12-14 hours. The present invention achieves this extension in time to peak plasma level as defined herein by tmax.

The invention also provides a controlled absorption diltiazem formulation for once-daily oral administration, comprising pellets as hereinbefore defined, said formulation including a sufficient quantity of a rapid release form of diltiazem so as to have a dissolution rate which when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 substantially corresponds to the following dissolution pattern:

a) from 5 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 10 to 60% of the total diltiazem is released after 4 hours of measurement in said apparatus;
c) from 30 to 90% of the total diltiazem is released after a total of 8 hours of measurement in said apparatus;
d) from 60 to 100% of the total diltiazem is released after 13 hours of measurement in said apparatus; and
e) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

Preferably, the once-daily formulation comprises a blend of pellets as hereinbefore defined together with up to 25% by weight of said rapid release form of diltiazem.

Most preferably, the rapid release form of diltiazem comprises pellets as hereinbefore defined without said membrane.

Preferably, the diltiazem is in the form of a pharmaceutically acceptable salt thereof, more particularly the hydrochloride salt thereof.

The organic acid is preferably represented by one or more of the following acids: adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid or tartaric acid. Especially preferred acids are adipic acid, fumaric acid and succinic acid. The diltiazem component and organic acid are preferably present in a ratio of from 10:1 and 2:1, more especially 6:1 to 3:1.

The core also optionally contains a lubricant which is represented by one or more of the following: sodium stearate, magnesium stearate, stearic acid or talc. The diltiazem and lubricant are preferably present in a ratio of from 5:1 to 100:1 for the once-daily formulation. The preferred diltiazem and lubricant ratio for the twice-daily formulation is from 0.5:1 to 45:1.

Preferably, the core comprises diltiazem or a pharmaceutically acceptable salt thereof and the associated organic acid embedded in a polymeric material. The diltiazem component and polymeric material are preferably present in a ratio of from 1:1 to 100:1, more particularly from 5:1 to 30:1. The polymeric material may be rapidly soluble in water or, alternatively, may be freely permeable to diltiazem and water.

Suitably, the core comprises:

a) a powder mixture containing diltiazem or a pharmaceutically acceptable salt thereof, an organic acid selected from adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid and tartaric acid, and

b) a polymeric material containing a major proportion of a pharmaceutically acceptable water soluble synthetic polymer and a minor proportion of a pharmaceutically acceptable water insoluble synthetic polymer,
said core comprising layers of said powder mixture and said polymeric material superimposed one upon the other and said polymeric material being present in an amount effective to ensure that all of said powder mixture is coated into said core.

The term water soluble polymer as used herein includes polymers which are freely permeable to water such as Eudragit RL. Likewise, the term water insoluble polymer as used herein includes polymers which are slightly permeable to water such as Eudragit RS.

The polymeric material preferably consists solely of a water soluble polymer or a polymer which is freely permeable to diltiazem and water. Alternatively, the polymeric material of the core may include a minor proportion of water insoluble polymer or a polymer which is slightly permeable to diltiazem and water. The ratio of water soluble/freely permeable to water insoluble/slightly permeable polymer is determined by the particular combination of polymers selected. However, in the case of a core including a water soluble polymer and a water insoluble polymer, the ratio of water soluble polymer to water insoluble polymer will normally be in the range of 1:1 to 50:1, more especially 3:1 to 9:1.

The water soluble polymer is suitably polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose or polyethylene glycol or a mixture thereof. An especially preferred water soluble polymer is polyvinylpyrrolidone.

A suitable polymer which is freely permeable to diltiazem and water is a polymer sold under the Trade Mark EUDRAGIT RL.

The water insoluble polymer is suitably ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), and poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate),

poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride) or polyurethane or a mixture thereof.

A suitable polymer which is slightly permeable to diltiazem and water is a polymer sold under the Trade Mark EUDRAGIT RS or a polymer whose permeability is pH dependent and sold under the Trade Mark EUDRAGIT L, EUDRAGIT S or EUDRAGIT E.

EUDRAGIT polymers are polymeric lacquer substances based on acrylates and/or methacrylates.

Polymeric materials sold under the Trade Marks EUDRAGIT RL and EUDRAGIT RS are acrylic resins comprising copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups and are described in the "EUDRAGIT" brochure of Messrs. Rohm Pharma GmbH (1985) wherein detailed physical-chemical data of these products is given. The ammonium groups are present as salts and give rise to the permeability of the lacquer films. EUDRAGIT RL and RS are freely permeable (RL) or slightly permeable (RS), respectively, independent of pH.

EUDRAGIT L is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester. It is insoluble in acids and pure water. It becomes soluble in a neutral to weakly alkaline milieu by forming salts with alkalis. The permeability of EUDRAGIT L is pH dependent. Above pH 5.0, the polymer becomes increasingly permeable. EUDRAGIT L is described in the "EUDRAGIT L" brochure of Messrs. Rohm Pharma GmbH (1986) wherein detailed physical-chemical data of the product is given.

The core suitably has between 50 and 200 layers of the core-forming materials and is built up in a manner known per se.

Preferably, the multi-layer arrangement of diltiazem, organic acid and polymeric material is built up on a central inert core in a conventional coating pan. The core suitably consists of a non-pareil bead or seed of sugar/starch having an average diameter in the range 0.4-0.8 mm, especially 0.5-0.6 mm for a twice-daily formulation and especially 0.6-0.71 mm for a once-daily formulation. Alternatively, the diltiazem, organic acid and polymeric material may be built up on a central inert core as hereinbefore defined in an automated coating system, for example, a CF granulator.

The core may also include further components to those specified above such as a dispersing agent, glidant and/or surfactant.

The diltiazem, organic acid and optional other components are blended to form a homogenous powder. The blend is suitably passed through an appropriate mesh screen using a milling machine. In the case of coating in a conventional coating pan, alternate layers of a coating solution/suspension of the polymeric material and the powder are applied to the central inert core so as to build up the multi-layer arrangement of the active core.

In the case of an automatic coating system, the coating solution/suspension of the polymeric material and the powder are applied simultaneously, in conventional manner. The coating solution/suspension of the polmeric material comprises one or more polymers dissolved/suspended in a suitable solvent or mixture of solvents. The concentration of the polymeric material in the coating solution/suspension is determined by the viscosity of the final solution/suspension. Preferably, between 10 and 40 parts of inert cores are used relative to the homogenous powder. The addition of a plasticizing agent to the polymeric solution/suspension may be necessary depending on the formulation to improve the elasticity and also the stability of the polymer film and to prevent changes in the polymer permeability over prolonged storage. Such changes could affect the drug release rate. Suitable plasticizing agents include polyethylene glycol, propylene glycol, glycerol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl citrate, castor oil and varying percentages of acetylated monoglycerides.

Preferred coating materials include - solutions/suspension of the polymers cited for use in the application of the powder blend to the central inert core in a suitable organic/aqueous carrier medium.

As indicated above, the membrane of the film-forming polymer or mixture of polymers surrounding the core preferably has a major proportion of a water insoluble polymer and optionally a minor proportion of a water soluble polymer, the ratio of water insoluble to water soluble polymer (when present) being determined by the inherent solubility characteristics of the polymer selected.

The membrane may also be composed of a proportion of a polymer which is slightly permeable to diltiazem and water and a proportion of a polymer which is freely permeable to diltiazem and water, the ratio of slightly permeable to freely permeable polymer being determined by the inherent permeability of the respective polymers. The terms "water soluble" and "water insoluble" polymer embrace such polymers as indicated above.

A suitable combination of a polymer which is slightly permeable to diltiazem and water and a polymer which is freely permeable to diltiazem and water is EUDRAGIT RS and EUDRAGIT RL in a ratio of from 1:1 to 50:1, especially 2:1 to 10:1. The membrane may also include a combination of water soluble/water insoluble polymers and polymers which are freely permeable/slightly permeable to diltiazem and water.

The membrane may also comprise a mixture of polymers that are water soluble, freely permeable, water insoluble, slightly permeable and polymers whose permeability/solubility is affected by pH.

Especially suitable polymers for the membrane include:

Polyvinylpyrrolidone, ethylcellulose, Eudragit RL, Eudragit L, Eudragit E, Eudragit S, cellulose acetate and polyvinyl alcohol. Commercially available ready-made polymeric solutions/suspensions are also especially preferred. These ready made solutions/suspensions may optionally contain plasticizing agents to improve the polymer film as described previously. Examples of ready-made solutions/suspensions of polymeric material with or without plasticizing agent include Eudragit RL 30D, Eudragit L 30D, Eudragit E 12.5, Eudragit RL 12.5 P, Eudragit RS 12.5, (Eudragit being a Trade Mark of Rohm and Haas, whose technical brochures describe the differences between the products), Aquacoat (a Trade Mark of FMC Corporation) and Sure-lease (a Trade Mark of Colorcon Inc.).

The membrane may be built up by applying a plurality of coats of membrane polymer solution or suspension to the core as hereinafter described. The membrane solution or suspension contains the polymer(s) dissolved or suspended, respectively, in a suitable aqueous or organic solvent or mixture of solvents, optionally in the presence of a lubricant. Suitable lubricants are talc, stearic acid, magnesium stearate and sodium stearate. A particularly preferred lubricant is talc. The membrane, polymer or mixture of polymers may optionally include a plasticizing agent, the function and choice of which has been previously described.

Preferably, the number of coats of membrane solution or suspension applied is between 20 and 600. The dissolution rate achieved is proportionally slower as the number of membrane coats increases.

The membrane solution or suspension may be applied to the active cores in a conventional coating pan as indicated or, alternatively, using an automated system such as a CF granulator, for example a FREUND CF granulator, a GLATT fluidized bed processor, an AEROMATIC, a modified ACCELA-COTA or any other suitably automated bead coating equipment (FREUND, GLATT, AEROMATIC and ACCELA-COTA are all Trade Marks).

Preferably 2-25 ml of membrane solution/suspension is applied per coat per kilogram of active cores. In an automated system the total amount of membrane solution/suspension applied to the active cores is the same as that applied in a conventional coating pan, expect that the membrane solution/suspension is applied continuously.

Preferably, when a coating pan is used the membrane is applied at a rate of 20-30 coats between each drying step until all of the coats have been applied. Between applications the pellets are dried for more than 12 hours at a temperature of 50-60°C, most suitably 55°C.

In an automated system the membrane is preferably applied at a rate which is equivalent to the application of 20-30 coats/day. After each application of this amount of membrane solution/suspension, the pellets are dried at the temperature and for the length of time specified for coating in a coating pan.

In an automated coating system the rate of application of membrane solution/suspension is suitably 0.5-10 g/kg of cores/min. The rate of application of lubricant such as talc is also suitably 0.5-10 g/kg of cores/min.

The pellets may be filled into hard or soft gelatine capsules. The pellets may also be compressed into tablets using a binder and/or hardening agent commonly employed in tabletting such as microcrystalline cellulose sold under the Trade Mark "AVICEL" or a co-crystallised powder of highly modified dextrins (3% by weight) and sucrose sold under the Trade Mark "DI-PAC" in such a way that the specific dissolution rate of the pellets is maintained.

In the management of cardiovascular disorders, it is often beneficial and desirable to target one or more vectors of the intricate internal blood pressure control system in order to achieve maximum therapeutic effect. For example, in addition to blocking the influx of calcium ions it may be desirable to inhibit angiotension converting enzyme (ACE), the activity of which is known to increase blood pressure by promoting vasoconstriction of the arterioles and sodium retention. To this end, this invention also relates to a pharmaceutical formulation of diltiazem and an ACE-inhibitor in an oral dosage form suitable for concomitant and combined administration providing for controlled release over a 24 hour period when given once or twice daily.

For combined use, the ACE-inhibitor or pharmaceutically acceptable salt thereof and the diltiazem or pharmaceutically acceptable salt thereof as defined herein are contained in a single dosage form to achieve desired plasma profiles for either once-daily or twice-daily administration.

The ACE-inhibitor can be combined with the sustained release diltiazem formulations either as pure active ingredient or active cores produced substantially in the same manner as discussed above for the diltiazem active cores. Both the diltiazem and the ACE-inhibitor may be formulated in the same active core.

For concomitant use, the ACE-inhibitor or pharmaceutically acceptable salt thereof and the diltiazem or pharmaceutically acceptable salt thereof as defined herein are contained in discrete dosage forms to achieve desired plasma profiles for either once-daily or twice-daily administration of the two active ingredients.

In a once-daily formulation, the amount of ACE-inhibitor present is no greater than that amount given as the normal daily dosage. It follows that a twice-daily formulation contains half the amount of ACE-inhibitor given as the normal daily dosage. Normally, the ratio of diltiazem to ACE-inhibitor will be between 50:1 and 1:5, preferably 20:1 to 1:1.

As will be appreciated, however, by those skilled in the art, both drugs exert an effect on the cardiovascular system but through different routes of action. For example, in controlling hypertension, each drug may be used in combination in daily amounts less than that which would be used when each drug is used alone.

Suitable ACE-inhibitors include captopril, losenopril, enalapril, ramipril, zofenopril, quinapril, cilazapril, spirapril, fosinopril, delapril, pivalopril, fentiapril, indolapril, alacepril, tiapamil (N-(3,4-dimethoxyphenethyl)-3-[2-(3,4-dimethoxyphe-

nyl)-1,3-dithian-2-yl]-N-methylpropylamine 1,1,3,3-tetraoxide), pentopril, rentiapril and perindopril.

Preferred ACE-inhibitors include captopril and enalapril.

According to a further aspect of the invention there is provided use of diltiazem or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the control of hypertension and the symptoms of angina over a twenty-four hour period following administration of a single therapeutically effective dose thereof. Furthermore, in accordance with the invention one may administer once-daily in combination or concomitantly with the diltiazem or pharmaceutically acceptable salt thereof a single therapeutically effective dose of an ACE-inhibitor as hereinabove defined.

In the accompanying drawings:

Fig. 1 is a graph of plasma levels (ng/ml) of diltiazem versus time after administration (hours) for the diltiazem formulation prepared in Example 13 (curve a) compared with a diltiazem formulation prepared in accordance with our EP-A-0 149 920 (curve b);

Fig. 2 is a graph of plasma levels (ng/ml) of diltiazem versus time after administration (hours) for the diltiazem formulation prepared in Example 14 (curve a) compared with a diltiazem formulation prepared in accordance with our EP-A-0 149 920 (curve b);

Fig. 3 is a graph of plasma levels (ng/ml) of diltiazem versus time after administration (hours) for the diltiazem formulation prepared in Example 15 (curve a) compared with conventional tablets (curve b);

Fig. 4 is a graph of dissolution (%) versus time (hours) of a batch of pellets prepared in accordance with Example 15, stored under ambient conditions as hereinafter described, and tested at different times after manufacture;

Fig. 5 is a graph of dissolution (%) versus time (hours) of a batch of pellets prepared in accordance with Example 15, 'stored' under accelerated conditions as hereinafter described and tested at different times after manufacture; and

Fig. 6 is a graph of dissolution (%) versus time (hours) of a batch of pellets prepared in accordance with Example 1 of our EP-A-0 149 920 'stored' under accelerated conditions as hereinafter described, and tested at different times after manufacture.

The invention will be further illustrated by the following Examples:-

EXAMPLE 1

Diltiazem hydrochloride (40 kg), fumaric acid (10 kg) and talc (4 kg) were blended and milled through a suitable mesh screen so as to obtain a homogenous powder.

The powder was applied to starch/sugar seeds (0.6-0.71 mm diameter) (10 kg) using a FREUND CF granulator and a coating solution of:

9% polyvinylpyrrolidone
in ethanol

A membrane was then applied to the active cores by spraying on a solution consisting of:

12.5% EUDRAGIT RS in acetone/isopropanol 40:60	40 parts by weight
12.5% EUDRAGIT RL in acetone/isopropanol 40:60	10 parts by weight
Isopropanol	50 parts by weight

while at the same time but separately dusting on talc (100 parts by weight) in conventional manner. The ratio of membrane solution to talc was 1:0.62 viz. 0.62 grams of talc is applied per gram of membrane solution. A sufficient amount of membrane solution and talc was applied to 50 kg of active cores to achieve the following dissolution profile given below.

The finished pellets were dried to evaporate all solvents prior to performing the dissolution test. The dissolution rate of the pellets was tested by the method of the U.S. Pharmacopoeia XXI Paddle Method in 0.05 M KCl, at pH 7.0 and at

100 r.p.m.

The diltiazem hydrochloride was quantitively determined using u.v. spectrophotometry at 237 nm. The dissolution rate was as follows:

Time (hours)	% Diltiazem Hydrochloride released
2	2.3
4	17.7
8	49.0
13	76.5
24	95.7

EXAMPLE 2

Example 1 was repeated except that the application of membrane-forming suspension was continued until the following dissolution profile was obtained.

The dissolution rate of the pellets so prepared was determined according to the procedure of Example 1 and was found to be as follows:

Time (hours)	% Diltiazem Hydrochloride release
2	0.8
4	13.8
8	52.6
13	80.4
24	98.1

EXAMPLE 3

Diltiazem hydrochloride (40 kg), fumaric acid (10 kg) and talc (4 kg) were blended and milled through a No. 50 mesh screen so as to obtain a homogenous powder.

The powder was applied to starch/sugar seeds (0.6-0.71 mm diameter) (10 kg) employing a granulator using a coating solution of:

9% polyvinylpyrrolidone
in ethanol

A membrane was then applied to the active cores by spraying on a solution consisting of:

12.5% EUDRAGIT RS in acetone/isopropanol 40:60	41 parts by weight
12.5% EUDRAGIT RL in acetone/isopropanol	10 parts by weight
Isopropanol	49 parts by weight

while at the same time but separately dusting on talc (100 parts by weight) in conventional manner. The ratio of membrane solution to talc applied was 1:0.62 viz. 0.62 grams of talc is applied per gram of membrane solution. A sufficient amount of membrane solution (includes solvents) and talc was applied to 50 kg of active cores to achieve a dissolution

rate of the pellets (determined in the manner set out in Example 1) as follows:

Time (hours)	% Diltiazem Hydrochloride released
2	0.7
4	16.8
8	62.9
13	87.6
24	98.7

An amount of the sustained release pellets so prepared (85% by weight of active ingredient) was combined with an amount (15% by weight of active ingredient) of immediate release pellets corresponding to active cores without the membrane. The dissolution rate of the blend so prepared was determined and was found to be as follows:

Time (hours)	% Diltiazem Hydrochloride released
2	24.70
4	40.30
8	70.10
13	89.30
24	98.90

EXAMPLE 4

Example 3 was repeated except that a sufficient amount of membrane solution (includes solvents) and magnesium stearate was applied to 50 kg of active cores, to achieve a dissolution rate of the pellets (determined in the manner set out in Example 1) as follows:

Time (hours)	% Diltiazem Hydrochloride released
2	0.35
4	5.10
8	33.90
13	69.60
24	95.20

An amount of the pellets (85% by weight) so prepared was combined with an amount of active cores (15% by weight), which active cores release all of their diltiazem hydrochloride in approximately 30 minutes and the dissolution rate of the blend so prepared was measured in the manner set out in Example 1 and was found to be as follows:

Time (hours)	% Diltiazem Hydrochloride released
2	11.30
4	15.75
8	49.50
13	81.85
24	96.95

EXAMPLE 5

Diltiazem hydrochloride (1.0 kg), adipic acid (0.5 kg) and talc (0.100 kg) were blended and milled through a No. 50 mesh screen so as to obtain a homogenous powder.

The powder was applied to starch/sugar seeds (0.6-0.71 mm diameter) (0.5 kg) in a standard coating pan using a coating solution of:

10% polyvinylpyrrolidone in isopropanol	80 parts by weight
5% ethylcellulose in isopropanol	20 parts by weight

The seeds were coated with a measured volume of coating solution followed by dusting on of a measured weight of the powder mix. The coated seeds were allowed to dry and the coating step repeated until all of the powder had been applied. The coated seeds defining active cores were then dried overnight to remove all traces of solvent.

The active cores of the pellets being prepared were then surrounded by a membrane solution consisting of:

5% ethylcellulose in isopropanol	90 parts by weight
5% polyvinylpyrrolidone in isopropanol	10 parts by weight

Each coat of membrane solution comprises 5 ml of solution per kg of coated seeds. After each coat had been applied the pellets were air dried in the coating pan.

The finished pellets were then subjected to a dissolution test. Prior to performing the dissolution test the pellets were dried to evaporate all of the solvent.

The dissolution rate of the pellets was tested by the method of U.S. Pharmacopoeia XXI (Paddle Method) according to the procedure of Example 1. The dissolution rate was as follows:

Time (hours)	% Diltiazem Hydrochloride released
2	1.50
4	11.20
8	45.60
13	75.30
24	95.10

EXAMPLE 6

Example 5 was repeated except that the coating solution used was:

7.5% cellulose acetate in isopropanol	20 parts by volume
7.5% polyvinylpyrrolidone in isopropanol	80 parts by volume

The membrane suspension used was:

7.5% polyvinylpyrrolidone in isopropanol	10 parts by volume
7.5% cellulose acetate in isopropanol	90 parts by volume
isopropanol	100 parts by volume
talc	100 parts by weight

The dissolution rate of the pellets, which was measured according to the procedure followed in Example 1 was found to be:

Time (hours)	% Diltiazem Hydrochloride released
2	0.10
4	8.50
8	42.10
13	65.70
24	94.50

EXAMPLE 7

Example 6 was repeated except that 0.75 kg starch/sugar seeds (0.05-0.6 mm) were used. The coating solution consisted of:

5% EUDRAGIT RL in acetone/isopropanol 40:60	80 parts by weight
5% EUDRAGIT RS in acetone/isopropanol 40:60	20 parts by weight

The membrane suspension consisted of:

5% EUDRAGIT RL in acetone/isopropanol 40:60	20 parts by weight
5% EUDRAGIT RS in acetone/isopropanol 40:60	40 parts by weight
5% EUDRAGIT L in acetone/isopropanol 40:60	40 parts by weight
Talc	100 parts by weight

The membrane suspension was applied and the product dried as in Example 5.
The dissolution rate was as follows:

Time (hours)	% Diltiazem Hydrochloride released
2	0.30
4	12.60
8	54.30
13	79.30
24	99.20

EXAMPLE 8

Diltiazem hydrochloride (3.067 kg) was blended together with an amount of sustained release pellets (39.932 kg) prepared in Example 3 along with Avicel pH101 (5.0 kg), cross- linked polyvinylpyrrolidone (1.75 kg) and magnesium stearate (0.25 kg).

The resulting blend was tabletted to obtain a tablet containing 240 mg diltiazem as the hydrochloride salt.

The dissolution rate of the tablets was tested by the method of the U.S. Pharmacopoeia XXI (Paddle Method) according to Example 1.

The dissolution rate was as follows:

Time (hours)	% Diltiazem Hydrochloride released
2	22.6
4	41.5
8	69.8
13	89.5
24	98.9

EXAMPLE 9

Diltiazem hydrochloride (3.0 kg), succinic acid (0.35 kg) and talc (0.3 kg) were blended and milled through a No. 100 mesh screen so as to obtain a homogenous powder.

The powder was applied to starch/sugar seeds (0.6-0.71 mm diameter) (0.75 kg) in a standard coating pan using a coating solution of:

9% polyvinylpyrrolidone
in isopropanol

The seeds were coated with a measured volume of coating solution followed by dusting on of a measured weight of the powder mix. The coated seeds were allowed to dry and the coating step repeated until all of the powder had been applied. The coated seeds defining the active cores of the pellet were then dried overnight to remove all traces of solvent.

The active cores of the pellet being prepared were then surrounded by a membrane by applying sequential coats of a suspension consisting of:

12.5% EUDRAGIT RS in acetone/isopropanol 40:60	53.33 parts by weight

(continued)

12.5% EUDRAGIT RL in acetone/isopropanol 40:60	13.33 parts by weight
Talc	33.33 parts by weight

After each coat had been applied the pellets were air dried in the coating pan.

Finished pellets were then subjected to a dissolution test. Prior to performing the dissolution test, the pellets were dried to evaporate all of the solvent. Application of the membrane-forming suspension and drying were continued until the following dissolution profile was obtained.

The dissolution rate of the pellets was tested by the method of U.S. Pharmacopoeia XXI (Paddle Method) in 0.05 M KCl at pH 7.0 and at 100 r.p.m.

The diltiazem hydrochloride was quantitatively determined using a uv spectrophotometer at 237 nm. The dissolution rate was as follows:

Time (hours)	% Diltiazem Hydrochloride released
2	1.7
4	10.7
8	50.6
13	79.9
24	101.4

EXAMPLE 10

Pellets were prepared using the ingredients and manufacturing process of Example 9 and having the following dissolution profile.

Time (h)	% Diltiazem Hydrochloride released
2	16.7
4	26.9
8	60.6
13	81.7
24	96.5

If desired, the same dissolution profile as given in Example 10 can be obtained by blending a proportion (5-20% by weight) of active cores with pellets as prepared in Example 9.

EXAMPLE 11

Example 1 was repeated except that 2.0 kg of diltiazem hydrochloride, 0.5 kg of fumaric acid and 0.2 kg of talc were used and a sufficient amount of membrane solution and talc was applied to achieve the following dissolution profile:

Time (h)	% Diltiazem Hydrochloride released
2	1.2
4	0.8
6	5.5
8	16.2
10	32.6
13	55.1
24	98.2

EXAMPLE 12

Example 11 was repeated except that a sufficient amount of membrane solution and talc was applied to achieve the following dissolution profile:

Time (h)	% Diltiazem Hydrochloride released
2	0.6
4	0.5
6	1.8
8	8.8
10	22.3
13	45.3
24	94.4

EXAMPLE 13

Diltiazem hydrochloride (10.0 kg), fumaric acid (2.5 kg) and talc (1.0 kg) were blended and milled through a No. 50 mesh screen so as to obtain a homogenous powder.

The powder was applied to starch/sugar seeds (0.6-0.71 mm diameter) (5.0 kg) in a standard coating pan using a coating solution of:

10% Polyvinylpyrrolidone in isopropanol	75 parts by weight
5% Ethylcellulose in methanol/methylene chloride 50/50	20 parts by weight
5% Polyvinylchloride in acetone	4.5 parts by weight
Dibutyl phthalate	0.1 parts by weight

The seeds were coated with a measured volume of coating solution followed by dusting on of a measured weight of the powder mix. The coated seeds were allowed to dry and the coating step repeated until all of the powder had been applied. The coated seeds were then dried at 45°C overnight.

The coated seeds defining the active core of the pellets being prepared were then surrounded by an outer mem-

brane consisting of:

5% Eudragit RS in acetone/isopropanol	80 parts by weight
5% Eudragit RL in acetone/isopropanol	15 parts by weight
5% Polyvinylchloride in acetone	5 parts by weight
Talc	99 parts by weight
Dibutyl phthalate	1 part by weight

A volume equivalent to 5 ml per kg of coated seeds was applied to the seeds in a standard coating pan. After each coat had been applied the pellets were air dried in the coating pan.

At regular intervals the pellets were placed in an oven and allowed to dry for more than twelve hours.

The pellets were then returned to the coating pan and the process of coating, followed by drying to remove solvents, was continued.

The finished pellets were then subjected to a dissolution test. The dissolution rate of the pellets was tested by the method of U.S. Pharmacopoeia XXI (Paddle Method) in 0.05 M KCl adjusted to pH 7.0 and was found to be as follows:

Time (hours)	% Diltiazem hydrochloride released
2	8.7
6	62.8
13	92.0

EXAMPLE 14

Example 13 was repeated except starch/sugar seeds 0.5-0.6 mm were used.

The coating solution used was:

17.5% Polyvinylpyrrolidone in isopropanol	90 parts by weight
10.0% Cellulose acetate in methylene chloride	10 parts by weight

The membrane suspension used was:

12.5% Eudragit RS in acetone/isopropanol	90 parts by weight
12.5% Eudragit RL in acetone/isopropanol	10 parts by weight
Talc	100 parts by weight
Isopropanol	100 parts by weight

At regular intervals the pellets were placed in an oven and dried at 55°C for more than twelve hours to remove solvents as in Example 13. The dissolution rate was tested according to the U.S. Pharmacopoeia XXI (Paddle Method). The results were as follows:

Time (hours)	% Diltiazem hydrochloride released
2	28.0
6	69.0
13	94.0

EXAMPLE 15

Diltiazem hydrochloride (40 kg), fumaric acid (10 kg) and talc (4.0 kg) were blended and milled through a No. 50 mesh screen so as to obtain a homogenous powder.

The powder so obtained was applied to starch/sugar seeds (20 kg) 0.5-0.6 mm in diameter, in a FREUND CF granulator using a coating solution of:

9.0% Polyvinylpyrrolidone in isopropanol

The seeds were coated with a measured volume of coating solution followed by dusting on of a measured weight of the powder mix. The coated seeds were allowed to dry and the coating step repeated until all of the powder had been applied. The coated seeds were then dried at 55°C overnight to remove solvent.

The coated seeds defining the active core of the pellet being prepared were then surrounded by an outer membrane. The membrane suspension used was:

12.5% Eudragit RS in acetone/isopropanol	80 parts by weight
12.5% Eudragit RL in acetone/isopropanol	20 parts by weight
Talc	100 parts by weight
Isopropanol	100 parts by weight

The seeds were then coated in a CF granulator with the membrane suspension and dried at regular intervals at 55°C for 16 hours to remove solvents.

The finished pellets were then subjected to a dissolution test. The dissolution rate of the pellets was tested by the method of U.S. Pharmacopoeia XXI (Paddle Method) in 0.05 M KCl adjusted to pH 7.0 and was found to be as follows:

Time (hours)	% Diltiazem hydrochloride released
2	22.3
6	65.4
13	88.0

EXAMPLE 16

Diltiazem hydrochloride (3.0 kg), succinic acid (0.5 kg) and talc (0.3 kg) were blended and milled through a No. 50 mesh screen so as to obtain a homogenous powder.

The powder was applied to starch/sugar seeds (0.6-0.71 mm diameter) (0.75 kg) in a standard coating pan using a coating solution of:

9% Polyvinylpyrrolidone in isopropanol	100 parts by weight

The active cores of the pellet being prepared were then surrounded by a membrane by applying coats of a suspension consisting of:

12.5% EUDRAGIT RS in acetone/isopropanol 40:60	20 parts by weight
12.5% EUDRAGIT RL in acetone/isopropanol 40:60	20 parts by weight
12.5% EUDRAGIT L in acetone/isopropanol 40:60	10 parts by weight
Talc	49 parts by weight
Dimethyl phthalate	1 part by weight

After each coat had been applied the pellets were air dried in the coating pan. At regular intervals the pellets were placed in an oven and dried at 55°C for more than twelve hours to remove solvent as in Example 13.

Finished pellets were then subjected to a dissolution test. The dissolution rate of the pellets was tested by the method of the U.S. Pharmacopoeia XXI (Paddle Method) in 0.05 M KCl at pH 7.0 and at 100 r.p.m.

The dissolution rate was as follows:

Time (hours)	% Diltiazem hydrochloride released
2	16.9
6	63.4
13	89.6

EXAMPLE 17

Diltiazem hydrochloride (40 kg), fumaric acid (10 kg) and talc (4 kg) were blended and milled through a No. 50 mesh screen.

The powder was applied to starch/sugar seeds (0.5-0.6 mm diameter) with a FREUND CF granulator using a coating solution of:

8% Polyvinylpyrrolidone in ethanol	90 parts by weight
10% Ethocel (Ethocel is a Trade Mark) in isopropanol	9.8 parts by weight
Diethyl phthalate	0.2 parts by weight

A membrane was then applied to the active cores by spraying on a suspension consisting of:

12.5% EUDRAGIT RL in acetone/isopropanol 40:60	10 parts by weight
12.5% EUDRAGIT RS in acetone/isopropanol 40:60	40 parts by weight

(continued)

Isopropanol	48.75 parts by weight
Tributyl citrate	1.25 parts by weight

While simultaneously but separately dusting on talc (100 parts by weight) in conventional manner.

A sufficient amount of membrane suspension and talc was applied to achieve a dissolution rate of the pellets, when measured according to U.S. Pharmacopoeia XXI (Paddle Method) as per Example 13, as follows:

Time (hours)	% Diltiazem hydrochloride released
2	24.3
6	71.6
13	98.3

EXAMPLE 18

Example 16 was repeated except the application solution consisted of:

5% Hydroxypropylmethyl cellulose in methanol/methylene chloride	99 parts by weight
Propylene glycol	1 part by weight

and the membrane suspension used was

10% Cellulose acetate in acetone	90 parts by weight
5% Polyethylene glycol in acetone	10 parts by weight

Talc was added as per Example 16.

A sufficient quantity of membrane suspension was applied to the pellets to achieve the following dissolution rate, all pellets having been dried to remove solvents.

Time (hours)	% Diltiazem hydrochloride released
2	13.8
6	61.3
13	88.6

EXAMPLE 19

Diltiazem hydrochloride (2.4 kg) and enalapril (0.2 kg) were blended together with an amount of sustained release pellets (41.53 kg) prepared in Example 3 along with Avicel pH101 (5.0 kg), cross-linked polyvinylpyrrolidone (1.75 kg) and magnesium stearate (0.25 kg).

The resulting blend was tabletted to obtain a tablet containing 120 mg of diltiazem hydrochloride and 10 mg of enalapril, which produced a dissolution and bioprofile suitable for once-daily administration of both active ingredients.

EXAMPLE 20

Fumaric acid (2 kg) was size reduced in a conventional pharmaceutical hammer mill through a No. 100 mesh screen. The milled fumaric acid was then blended with captopril (6 kg) for twenty minutes. A solution of polyvinylpyrrolidone (P.V.P.) and ethylcellulose (Ethocel - Ethocel is a Trade Mark) in isopropanol was prepared at concentrations of 15% and 2% of the respective components.

Non-pareil seeds (5 kg) with a particle size of 0.5 to 0.6 mm were placed in a conventional pharmaceutical coating pan. The fumaric acid/captopril blend was applied onto the non-pareil seeds using the P.V.P./Ethocel solution as a binding agent. On completion of this operation the resulting active cores were transferred to a tray drying oven for solvent removal. 10% by weight of active ingredient of the foregoing active cores were mixed with pellets produced according to Example 3 except that the sustained release pellets from said Example contained 90% by weight of diltiazem hydrochloride and said immediate release pellets contained 15% by weight of diltiazem hydrochloride. After blending of the three pellet types they were filled into hard gelatin capsules, so that each capsule contained 120 mg of diltiazem hydrochloride and 50 mg of captopril.

EXAMPLE 21

An amount of pellets as prepared in Example 13 was mixed with an amount of active captopril cores and filled into hard gelatin capsules in a ratio such that the capsule contained 90 mg of diltiazem hydrochloride and 37.5 mg of captopril.

Pharmacological Data for Once-Daily

EXAMPLE 14

In Vivo Performance:

Pharmacological Data for the Diltiazem Formulation of Example 1

The pellet formulation prepared in Example 1 was evaluated in vivo under steady state conditions.

A steady-state study was performed in 12 young healthy male volunteers, comparing the formulation of Example 1 with a reference product (conventional immediate release tablets). The formulation of Example 1 was administered as a single 240 mg encapsulated dose at 0 hours, while the reference was administered as a single 60 mg tablet at 0, 6, 12 and 18 hours (i.e. q.i.d.). Plasma was sampled out to 24 hours and the mean results were calculated and tabulated.

The data presented in Table 1 are from day 5 sampling.

TABLE 1

Mean Diltiazem Concentrations (ng/ml) - Day 5		
Hour	Reference	Formulation of Example 1
0.00	104.08	74.83
0.50	104.17	75.25
1.00	140.75	72.17
2.00	185.42	71.75
3.00	-	72.67
4.00	139.83	88.42
6.00	107.00	95.42
6.50	93.42	-
7.00	107.42	-
8.00	143.58	96.92
10.00	138.00	107.50

TABLE 1 (continued)

Mean Diltiazem Concentrations (ng/ml) - Day 5		
Hour	Reference	Formulation of Example 1
12.00	94.42	106.75
12.50	77.42	-
13.00	87.83	-
13.50	92.58	-
14.00	109.42	109.17
16.00	109.00	107.75
18.00	82.33	96.25
18.50	81.45	-
19.00	94.00	-
20.00	120.33	85.00
22.00	117.75	-
24.00	98.92	71.08

DISCUSSION

The results of this in vivo comparison of the formulation of Example 1 against conventional immediate release tablets (reference) indicate the formulation of

Example 1 to be bioequivalent (85%) to reference (100%). The formulation of Example 1 also exhibits reduced peak to trough fluctuations, thus enabling titration of the dose to safe, consistent and efficacious plasma levels, which is not always seen with more frequently administered immediate release forms of diltiazem. However, the main distinguishing feature is the tmax (time to peak plasma levels) which is considered to be the single most important pharmacokinetic criterion for characterising a specific dosage frequency. The tmax for the formulation of Example 1 is 14.00 hours, thus indicating suitability thereof for once-daily administration, while the tmax for reference is 2.75 hours. Furthermore, when compared to the formulation of Example 1 of our EP-A-0 149 920, a diltiazem formulation for twice-daily administration and having a tmax of 6.7 hours, the extension of tmax achieved with the once-daily formulation of the present invention becomes apparent.

Pharmacological Data for the Diltiazem Formulation of Example 2

METHOD

Subjects:

Six male volunteers participated in the study (Table 2). One subject (Subject 2) dropped out after the second leg of the study for reasons unrelated to participation in the study. All subjects were shown to be healthy during a prestudy physical examination. Volunteers denied use of any medication during the 14 days prior to study initiation.

TABLE 2

Subject Number	Subject Initials	Age Yrs	Height Cms	Weight (Kg)	Smoker
1	SF	21	171.5	72.8	Yes
2	NH	21	173.0	65.0	No
3	LH	25	174.0	70.0	No
4	PB	21	172.0	61.5	Yes

TABLE 2 (continued)

Subject Number	Subject Initials	Age Yrs	Height Cms	Weight (Kg)	Smoker
5	GG	19	180.0	74.0	Yes
6	TS	40	165.0	77.0	No

Medication and Dosing

The following medication was used in the study:

(1) Reference 30 mg tablets

(2) Diltiazem 120 mg capsules prepared from a blend of sustained release pellets prepared in Example 2 with 5% of immediate release pellets viz the sustained release pellets without the membrane, hereinafter designated as the formulation of Example 2.

The reference was administered as a 30 mg dose at 0, 6, 12 and 18 hours. The formulation of Example 2 in capsule form was given as a single 120 mg dose at 0 hours.

The studies were designed as a randomized, balanced, single-dose two-way crossover comparison of the reference and the diltiazem formulation of Example 2.

The trial was initially divided into two 24-hour treatment periods. A third 24-hour treatment period was then performed. There were seven days separating each study period. At the time of study entry, subjects were randomly given a study number from 1 to 6, and assigned to treatment schedules based on that study number as shown in Table 3.

Volunteers arrived at the study site 10 to 12 hours before dosing and remained in a fasted state for at least 8 hours before and until 3 hours after dosing. Diet was standardized among treatment periods.

TABLE 3

Subject Numbers	TREATMENT PERIODS	
	1	2
1, 2, 3	Reference	Formulation of Example 2
4, 5, 6	Formulation of Example 2	Reference

Plasma diltiazem concentrations were determined by high performance liquid chromatography.

RESULTS

Plasma Diltiazem Concentrations

A summary of the mean results is presented in Table 4.

TABLE 4

Mean Diltiazem Concentrations (ng/ml)		
Time	Reference	Formulation of Example 2
0.0	0.0	0.0
0.5	4.02 ± 3.31	---
1.0	12.98 ± 9.36	6.10 ± 2.20
2.0	20.80 ± 11.15	6.88 3.17
3.0	23.60 ± 11.15	---

TABLE 4 (continued)

Mean Diltiazem Concentrations (ng/ml)		
Time	Reference	Formulation of Example 2
4.0	22.00 ± 10.25	16.32 ± 7.23
6.0	15.68 ± 5.87	21.58 ± 13.33
6.5	15.82 ± 7.16	---
7.0	29.04 ± 15.29	30.60 ± 9.56
8.0	38.00 ± 10.46	35.80 ± 13.39
9.0	---	40.80 ± 18.90
10.0	32.00 ± 7.97	46.20 ± 20.78
12.0	21.60 ± 6.39	54.60 ± 26.43
12.5	18.40 ± 6.66	---
13.0	21.75 ± 9.10	---
14.0	33.60 ± 14.47	56.00 ± 25.42
16.0	34.60 ± 11.72	45.60 ± 16.96
18.0	26.80 ± 5.97	39.20 ± 13.99
18.5	26.60 ± 7.33	---
19.0	27.40 ± 12.92	---
20.0	38.20 ± 17.02	28.40 ± 5.27
22.0	34.20 ± 9.88	---
24.0	39.20 ± 14.86	22.80 ± 7.29
28.0	17.02 ± 4.75	---
36.0	2.58 ± 3.55	3.54 ± 3.38

DISCUSSION

The purpose of the studies carried out was to compare the pharmacokinetic profiles of a controlled absorption formulation of diltiazem according to the invention with divided doses of a reference product. The formulation of Example 2 was especially designed for once-daily administration of diltiazem and it was anticipated that this formulation would demonstrate a plasma profile consistent with this reduced dosage frequency.

The results of the study confirm the delayed and extended plasma profile of the formulation of Example 2. Although the product of Example 2 contains a proportion of immediate-release component (5%), the product demonstrated a significantly delayed time to peak plasma diltiazem concentrations compared with the reference. Mean trough levels were very similar for both products with no significant differences in mean blood concentrations at 24 hours post administration for the product of Example 2 relative to the reference, further emphasizing the prolonged absorption nature of the formulation according to the invention.

The elimination characteristics of the formulation of Example 2 were also consistent with a once-daily plasma profile. The formulation of Example 2 showed a considerably slower apparent elimination rate and longer apparent half-life value compared with the reference.

Estimates of relative bioavailability showed the formulation of Example 2 to be more bioavailable than the reference product demonstrating 112.05% relative bioavailability based on 24 hour data.

The formulation of Example 2 attained a remarkably extended tmax of 13.20 hours after administration as compared to 2.30 hours for reference and 8.7 hours for the formulation of Example 1 of our EP-A-0 149 920, which is a diltiazem formulation suitable for twice-daily administration. This extension in tmax thus shows the formulation of Example 2 to meet the criteria for once-daily administration and the overall results of the study demonstrate the achievement of a once-daily profile for the product of Example 2.

Pharmacological Data in respect of the Formulation of Example 3

The blend of pellets prepared in Example 3 was filled into hard gelatine capsules so as to give capsules containing 120 mg diltiazem hydrochloride. A single dose of the capsules so prepared was compared with a single dose of pellets in capsule form and which pellets are prepared in accordance with Example 1 of our EP-A-0 149 920 (twice-daily form of diltiazem) and identified hereinafter as "twice-daily formulation" administered as a single dose in six subjects. The two different formulations were tested in the same group of six subjects. The mean blood levels of the two formulations were determined and are shown in Table 5.

TABLE 5

Time(h)	Twice-daily Formulation Blood Level (ng/ml)	Time(h)	Formulation of Example 3 Blood Level (ng/ml)
0.00	0.00	0.00	0.00
1.00	0.00	1.00	11.20
2.00	2.17	2.00	12.30
4.00	29.67	4.00	17.97
5.00	52.33	5.00	22.67
6.00	63.67	6.00	28.67
7.00	69.00	7.00	32.33
8.00	69.50	8.00	36.17
9.00	62.50	9.00	38.50
10.00	53.83	10.00	44.50
12.00	38.67	12.00	41.67
14.00	27.17	14.00	35.33
16.00	20.17	16.00	28.33
18.00	15.22	18.00	23.00
20.00	12.95	20.00	18.33
24.00	7.70	24.00	12.77

Time of Maximum Blood Levels (tmax)

The time of maximum blood levels (h) (tmax) was observed for each subject and each formulation. The mean tmax values were as follows:

Twice-daily formulation	Mean tmax = 7.17	Based on 6 subjects
Formulation of Example 3	Mean tmax = 10.67	Based on 6 subjects

DISCUSSION

In the study, the formulation of Example 3 was compared with a formulation prepared as per Example 1 of our EP-A-0 149 920 which is an effective formulation for twice-daily administration of diltiazem. Whilst the "twice-daily" formulation achieves a notable extension in tmax (7.17 hours) as compared to conventional immediate release diltiazem, it does not exhibit a pharmacokinetic profile consistent with once- daily administration. However, the formulation of Example 3 demonstrates a lower peak to trough ratio than, while being bioequivalent (93.5%) to, the twice- daily formulation (100%). Most importantly, however, is the significantly extended tmax obtained (10.67 hours) with the formulation of Example 3, thus demonstrating an overall pharmacokinetic profile consistent with once-daily administration.

Pharmacological Data for the Diltiazem Hydrochloride Formulation prepared in Example 4

The blend of pellets prepared in Example 4 was filled into hard gelatine capsules so as to give capsules containing 120 mg diltiazem hydrochloride. A single dose of the capsules so prepared was compared with conventional reference tablets (30 mg) hereinafter referred to as reference administered four times daily in six subjects. The two different formulations were tested in the same group of six subjects.

The meant blood levels of the two formulations were determined and are shown in Table 6.

TABLE 6

Time(h)	Reference Blood Level (ng/ml)	Time(h)	Formulation of Example 4 Blood Level (ng/ml)
0.00	0.00	0.00	0.00
0.50	4.93	0.50	0.00
1.00	6.40	1.00	10.42
1.50	12.52	2.00	17.63
2.00	18.65	4.00	15.07
4.00	22.17	6.00	21.22
6.00	12.07	7.00	23.38
6.50	10.62	8.00	27.30
7.00	21.47	10.00	33.67
7.50	30.83	12.00	39.83
8.00	29.00	14.00	40.83
10.00	31.17	16.00	33.83
12.00	16.97	20.00	25.17
12.50	15.65	24.00	20.13
13.00	15.42	36.00	4.62
13.50	25.00	0.00	0.00
14.00	29.50	0.00	0.00
16.00	30.30	0.00	0.00
18.00	21.93	0.00	0.00
18.50	25.00	0.00	0.00
18.90	26.33	0.00	0.00
19.50	29.65	0.00	0.00
20.00	37.83	0.00	0.00
22.00	35.33	0.00	0.00
24.00	28.83	0.00	0.00

Time of Maximum Blood Levels (tmax)

The time of maximum blood levels (h) (tmax) was observed for each subject and each formulation.
The mean tmax values were as follows:

Reference	Mean tmax = 2.58	Based on 6 subjects
Formulation of Example 4	Mean tmax = 13.00	Based on 6 subjects

DISCUSSION

The formulation of Example 4 demonstrated a remarkably extended in vivo tmax (13.00 hours) as compared to reference (2.58 hours). Furthermore, the formulation of Example 4 was bioequivalent (100%) to conventional immediate release tablets administered every six hours (100%). Based on this overall pharmacokinetic profile, the formulation of Example 4 is eminently suitable for once-daily oral administration.

Pharmacological Data in respect of the Formulation of Examples 11 and 12

The pellets prepared in Examples 11 and 12 were filled into hard gelatine capsules so as to give capsules containing 120 mg diltiazem hydrochloride. A single dose of the capsules so prepared was administered as a single dose in five subjects. The time of maximum blood levels (h) (tmax) was observed for each subject and formulation and the mean tmax value for Example 11 was 17.8 and the mean tmax value for Example 12 was 18.6.

Pharmacological Data for Twice-Daily Diltiazem Formulations

In vivo Performance:

Pharmacological Data for the Diltiazem Formulation of Example 13

A single-dose crossover study was performed in 6 young healty male subjects comparing the formulation of Example 13 against the formulation of Example 1 of our EP-A-0 149 920 (hereinafter referred to as Reference). Both the formulation of Example 13 and the Reference formulation were administered as a single encapsulated dose of 120 mg at 0 hours. Plasma concentration of diltiazem was determined at intervals over 24 hours and the results are illustrated in Fig. 1.

Fig. 1 is a graph of plasma levels (ng/ml) of diltiazem versus time after administration (hours) for a single dose (120 mg) of the diltiazem formulation prepared in Example 13 (curve a) compared with a single dose (120 mg) of the Reference formulation (curve b). As will be appreciated, the data for the Reference formulation was obtained from a different group of subjects to that of present Example 13, thus making any comparison of bioavailability purely indicative. It will be observed from Fig. 1 that a virtually identical absorption pattern is obtained for each formulation, consistent with twice-daily administration. Hence it is submitted the actual bioavailability values would have been similar if the two formulations had been tested in the same subjects.

Pharmacological Data for the Diltiazem Formulation of Example 14

A single-dose crossover study was performed in 6 young healthy male subjects comparing the formulation of Example 14 against the formulation of Example 1 of our EP-A-0 149 920 (hereinafter referred to as Reference). Both formulations were administered as a single 120 mg capsule at 0 hours. Plasma concentration of diltiazem was determined at intervals over 24 hours and the results are illustrated in Fig. 2.

Fig. 2 is a graph of plasma levels (ng/ml) of diltiazem versus time after administration (hours) for a single dose (120 mg) of the diltiazem formulation prepared in Example 14 (curve a) compared with a single dose (120 mg) of the Reference formulation (curve b). As in the case of the pharmacological data for the formulation of Example 13 compared with the Reference, the data for the Reference formulation were obtained from a different group of subjects to that of present Example 14, thus making any comparison of bioavailability purely indicative. It will be observed from Fig. 2 that a virtually identical absorption pattern is obtained for each formulation, consistent with twice-daily administration. Hence it is submitted the actual bioavailability values would have been similar if the two formulations had been tested in the same subjects.

Pharmacological Data for the Diltiazem Formulation of Example 15

A steady-state crossover study was performed in 12 young healthy male subjects comparing the formulation of

Example 15 against conventional immediate release tablets (Reference tablets).

The formulation of Example 15 was administered as a single 120 mg capsule at 0 and 12 hours (b.i.d.), while the Reference was administered as a single 60 mg tablet of 0, 6, 12 and 18 hours (q.i.d.). Plasma concentration of diltiazem was measured at intervals over 24 hours on Day 5 and the results are illustrated in Fig. 3. Pharmacokinetic data are given in Table 7.

TABLE 7

PHARMACOKINETIC EVALUATION (n=6)		
Parameters	Reference Tablets	Formulation of Example 15
AUC (0-24h)	2474.88	2230.33
F (t) %	100.00	90.96
Cmax	172.08	130.42
Tmax	2.75	4.17

Fig. 3 is a graph of plasma levels (ng/ml) of diltiazem versus time after administration (hours) for a single dose (120 mg) of the diltiazem formulation prepared in Example 3 (curve a) compared with a single dose (60 mg) of reference tablets administered as indicated above.

It will be observed from the data presented in Table 7 that the formulation of Example 15 is 90.96% bioavailable compared to Reference (= 100%), and has a quite similar Cmax and AUC (0-24h). However, the formulation of Example 15 has extended tmax (4.17 hours compared to 2.75 hours for Reference) which satisfies the criteria for controlled absorption orally administered drugs, and further shows a reduction in peak-to-trough fluctuations as indicated in Fig. 3.

Experiments were carried out to assess the stability of the pellet formulation according to the invention relative to formulations of our EP-A-0 149 920.

Dissolution tests of the type described in Example 13 were carried out on a batch of the pellet formulation of Example 15 after storage in ambient conditions over a period concomitant with commercial shelf-life, in accordance with established criteria. The results are presented in Fig. 4 which is a graph of dissolution (%) versus time (hours) taken at three different time points after manufacture of the formulation of Example 15 under the indicated conditions and is indicative of the stability of the formulation under these conditions. In Fig. 4 curve a represents the batch as tested after 3 months of storage, curve b the batch as tested after 6 months storage and curve c the batch as tested after 18 months storage.

Dissolution tests of the type described in Example 13 were also carried out on a batch of the pellet formulation of Example 15 under 'accelerated conditions' (37°C and 75% relative humidity) in accordance with established criteria. The results are presented in Fig. 5 which is a graph of dissolution (%) versus time (hours) taken at three different time points after the manufacture of the formulation of Example 15 under the indicated conditions and is indicative of the stability of the formulation under these conditions. In Fig. 5 curve a represents the batch as tested after 1 month of storage, curve b the batch as tested after 3 months of storage and curve c the batch as tested after 6 months of storage.

Identical dissolution tests under identical accelerated conditions were carried out on a batch of a pellet formulation prepared in accordance with Example 1 of our EP-A-0 149 920. The results are presented in Fig. 6 which again is a graph of dissolution (%) versus time (hours) taken at three different time points after the manufacture of the formulation in question. In Fig. 6 curve a represents the batch as tested after 1 month of storage, curve b the batch as tested after 3 months of storage and curve c the batch as tested after 6 months of storage. A comparison of Figs. 4, 5 and 6 demonstrates the stability of the formulation of the present invention relative to the formulation of our EP-A-0 149 920. As will be observed the formulation of EP-A-0 149 920 under the specified conditions is unstable and therefore if commercially used would require excessive inventory control procedures.

The formulations according to the invention, which are characterised by specific in vitro dissolution rates and a more controlled manufacturing process, have excellent stability over the normal marketing shelf-life (18 months to 2 years) in terms of both in vivo and in vitro performance.

Claims

1. A controlled absorption diltiazem pellet formulation for oral administration, said pellet comprising a core of diltiazem or a pharmaceutically acceptable salt thereof in association with an organic acid, the diltiazem component and the organic acid being present in a ratio of from 50:1 to 1:1, and a multi-layer membrane surrounding said core and

containing a major proportion of a pharmaceutically acceptable film-forming, water insoluble synthetic polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble synthetic polymer, the number of layers in said membrane and the ratio of said water soluble to water insoluble polymer, when said water soluble polymer is present, being effective to permit release of said diltiazem from said pellet at a rate allowing controlled absorption thereof over, on the average, not less than a twelve hour period following oral administration, said rate being measured in vitro as a dissolution rate of said pellet, which when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 substantially corresponds to the following dissolution pattern:

a) no more than 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) no more than 60% of the total diltiazem is released after 4 hours of measurement in said apparatus; and
c) 100% of the diltiazem is released no earlier than after 8 hours of measurement in said apparatus.

2. A controlled absorption diltiazem pellet formulation according to Claim 1, wherein the release of diltiazem from said pellet is at a rate allowing controlled absorption thereof over a twenty-four hour period following oral administration, said rate being measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 which substantially corresponds to the following dissolution pattern:

a) from 0 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 0 to 45% of the total diltiazem is released after 4 hours of measurement in said apparatus;
c) from 10 to 75% of the total diltiazem is released after 8 hours of measurement in said apparatus;
d) from 25 to 95% of the total diltiazem is released after 13 hours of measurement in said apparatus; and
e) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

3. A controlled absorption diltiazem pellet formulation according to Claim 1, wherein the release of diltiazem from said pellet is at a rate allowing controlled absorption thereof over a twenty-four hour period following oral administration, said rate being measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 which substantially corresponds to the following dissolution pattern:

a) from 0 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 5 to 45% of the total diltiazem is released after 4 hours of measurement in said apparatus;
c) from 30 to 75% of the total diltiazem is released after 8 hours of measurement in said apparatus;
d) from 60 to 95% of the total diltiazem is released after 13 hours of measurement in said apparatus; and
e) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

4. A controlled absorption diltiazem pellet formulation according to Claim 1, wherein the release of diltiazem from said pellet is at a rate allowing controlled absorption thereof over a twelve hour period following oral administration, said rate being measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 which substantially corresponds to the following dissolution pattern:

a) from 5 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 35 to 85% of the total diltiazem is released after 6 hours of measurement in said apparatus; and
c) 100% of the total diltiazem is released no earlier than after 8 hours of measurement in said apparatus.

5. A controlled absorption diltiazem pellet formulation according to Claim 1, wherein the release of diltiazem from said pellet is at a rate allowing controlled absorption thereof over a twelve hour period following oral administration, said rate being measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 which substantially corresponds to the following dissolution pattern:

a) from 5 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 55 to 80% of the total diltiazem is released after 6 hours of measurement in said apparatus; and
c) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

6. A controlled absorption diltiazem pellet formulation according to any one of Claims 1 to 5, wherein the core comprises:

a) a powder mixture containing diltiazem or a pharmaceutically acceptable salt thereof, an organic acid selected from adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid and tartaric acid, and

b) a polymeric material containing a major proportion of a pharmaceutically acceptable water soluble synthetic polymer and a minor proportion of a pharmaceutically acceptable water insoluble synthetic polymer,
said core comprising layers of said powder mixture and said polymeric material superimposed one upon the other and said polymeric material being present in an amount effective to ensure that all of said powder mixture is coated into said core.

7. A controlled absorption diltiazem pellet formulation according to any one of Claims 1 to 6, wherein the water soluble polymer in the core or membrane is the same or different and is selected from polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose or polyethylene glycol or a mixture thereof.

8. A controlled absorption diltiazem pellet formulation according to any one of Claims 1 to 6, wherein the water soluble polymer in the core or membrane is replaced by a polymeric material which is freely permeable to diltiazem and water and comprises a copolymer of acrylic and methacrylic acid esters.

9. A controlled absorption diltiazem pellet formulation according to any one of Claims 1 to 8, wherein the water insoluble polymer in the core or membrane is selected from ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate poly (ethyl methacrylate), poly(butyl methacrylate), poly (isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride) or polyurethane or a mixture thereof.

10. A controlled absorption diltiazem pellet formulation according to any one of Claims 1 to 8, wherein the water insoluble polymer in the core or membrane is replaced by a polymeric material which is slightly permeable to diltiazem and water and comprises a copolymer of acrylic and methacrylic acid esters.

11. A process for the production of a controlled absorption diltiazem pellet formulation according to any one of Claims 1 to 10, which comprises forming a core of diltiazem, or a pharmaceutically acceptable salt thereof, an organic acid and other optional components and enclosing the core in a membrane of a film-forming polymer or mixture thereof as defined in Claim 1 which permits release of the diltiazem or the pharmaceutically acceptable salt thereof in the manner set out in any one of Claims 1 to 5.

12. A controlled absorption diltiazem formulation for oral administration comprising pellets according to any one of Claims 1 to 3 or any one of Claims 6 to 10 when dependent on any one of Claims 1 to 3, said formulation including a sufficient quantity of a rapid release form of diltiazem so as to have a dissolution rate which when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopoeia XXI in 0.05 M KCl at pH 7.0 substantially corresponds to the following dissolution pattern:

a) from 5 to 35% of the total diltiazem is released after 2 hours of measurement in said apparatus;
b) from 10 to 60% of the total diltiazem is released after 4 hours of measurement in said apparatus;
c) from 30 to 90% of the total diltiazem is released after 8 hours of measurement in said apparatus;
d) from 60 to 100% of the total diltiazem is released after 13 hours of measurement in said apparatus; and
e) not less than 85% of the total diltiazem is released after 24 hours of measurement in said apparatus.

13. A controlled absorption formulation for oral administration comprising pellets according to any one of Claims 1 to 10 and 12, further comprising an ACE-inhibitor or a pharmaceutically acceptable salt thereof, said ACE-inhibitor preferably being selected from captopril, fosenopril, enalapril, ramipril, zofenopril, quinapril, ciazapril, spirapril, lisinopril, delapril, pivalopril, fentiapril, indolapril, alacepril, tiapamil (N-(3,4-dimethoxyphenethyl)-3-[2-(3,4-dimethoxyphenyl)-1 3-dithian-2-yl]-N-methylpropylamine 1,1,3,3-tetraoxide), pentopril, rentiapril and perindopril.

14. Use of diltiazem or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the control of hypertension and the symptoms of angina over a twenty-four hour period following administration of a single

therapeutically effective dose thereof.

15. Use according to Claim 14, wherein there is administered once-daily in combination or concomitantly with the diltiazem or pharmaceutically acceptable salt thereof a single therapeutically effective dose of an ACE-inhibitor.

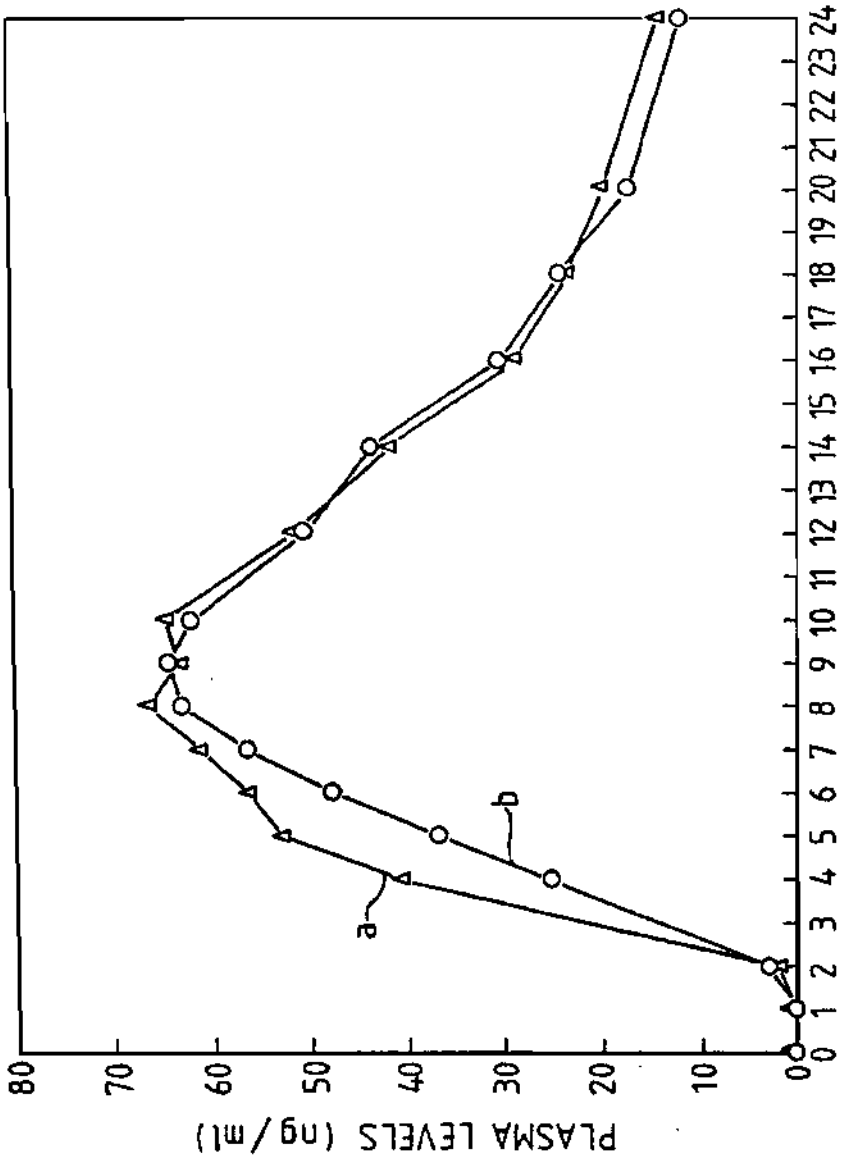

FIG. 1.

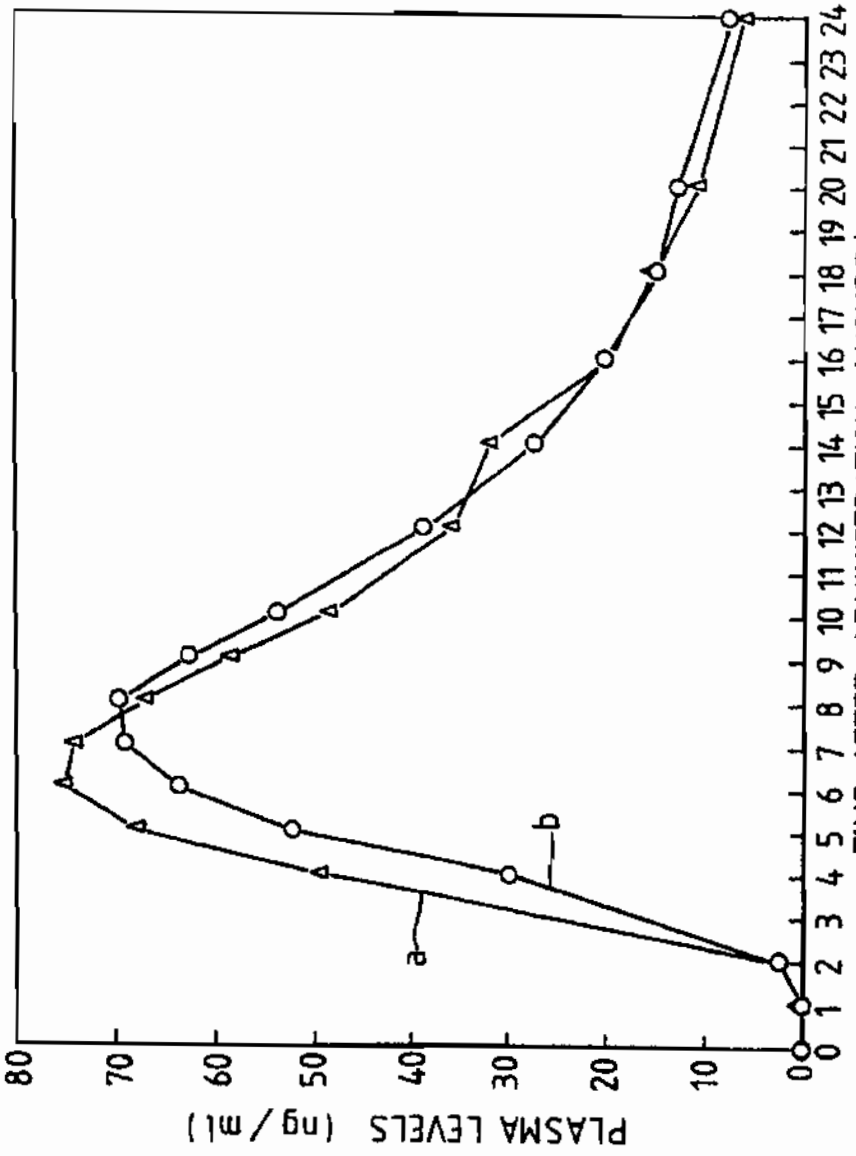

FIG. 2.

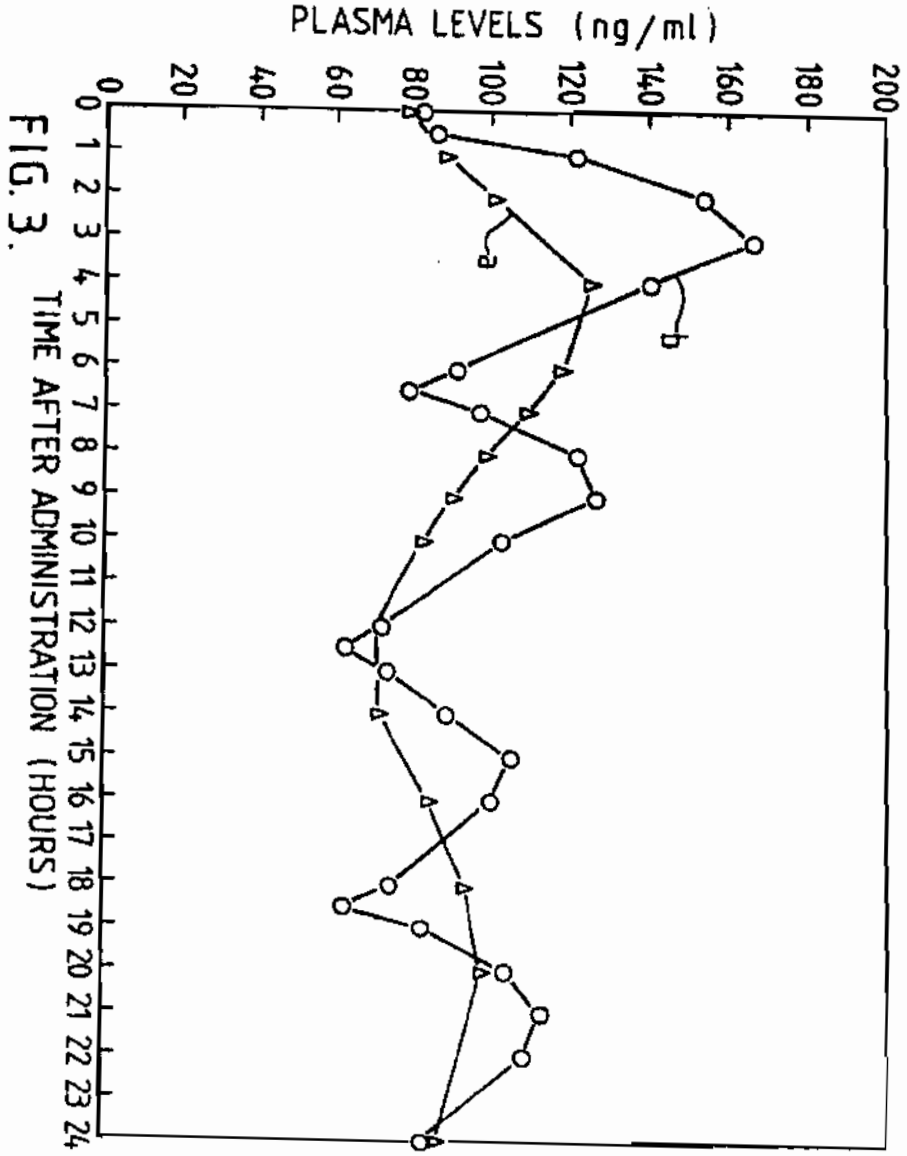
PLASMA LEVELS (ng/ml)
0
20
40
60
80
100
120
140
160
180
200
a
b
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
TIME AFTER ADMINISTRATION (HOURS)

FIG. 3.

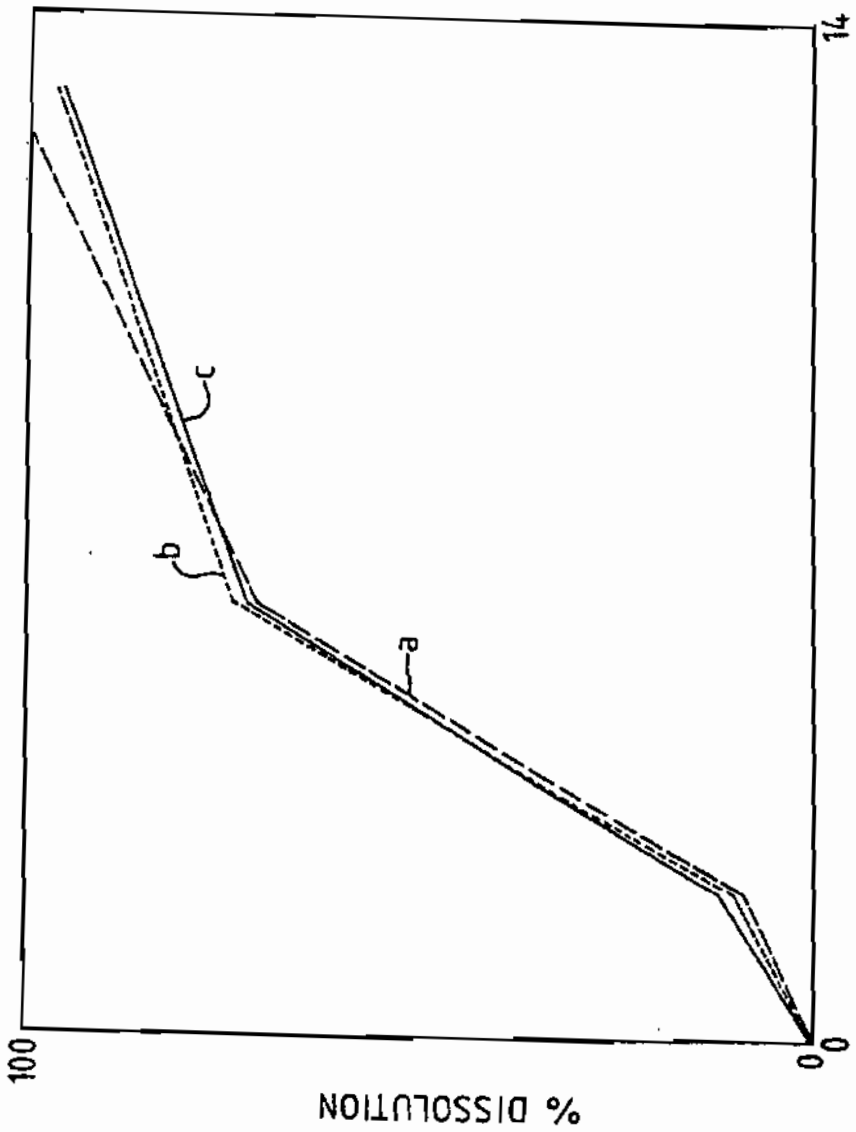

FIG. 4.

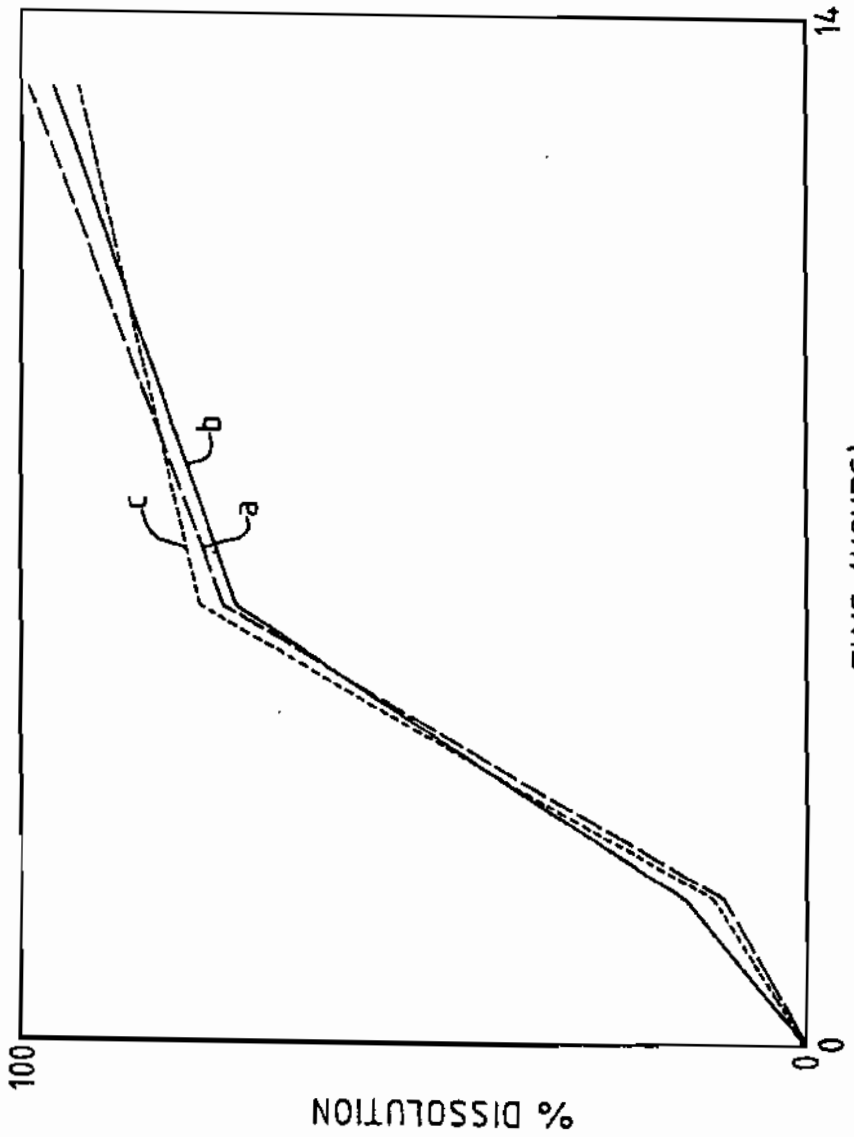

FIG. 5.

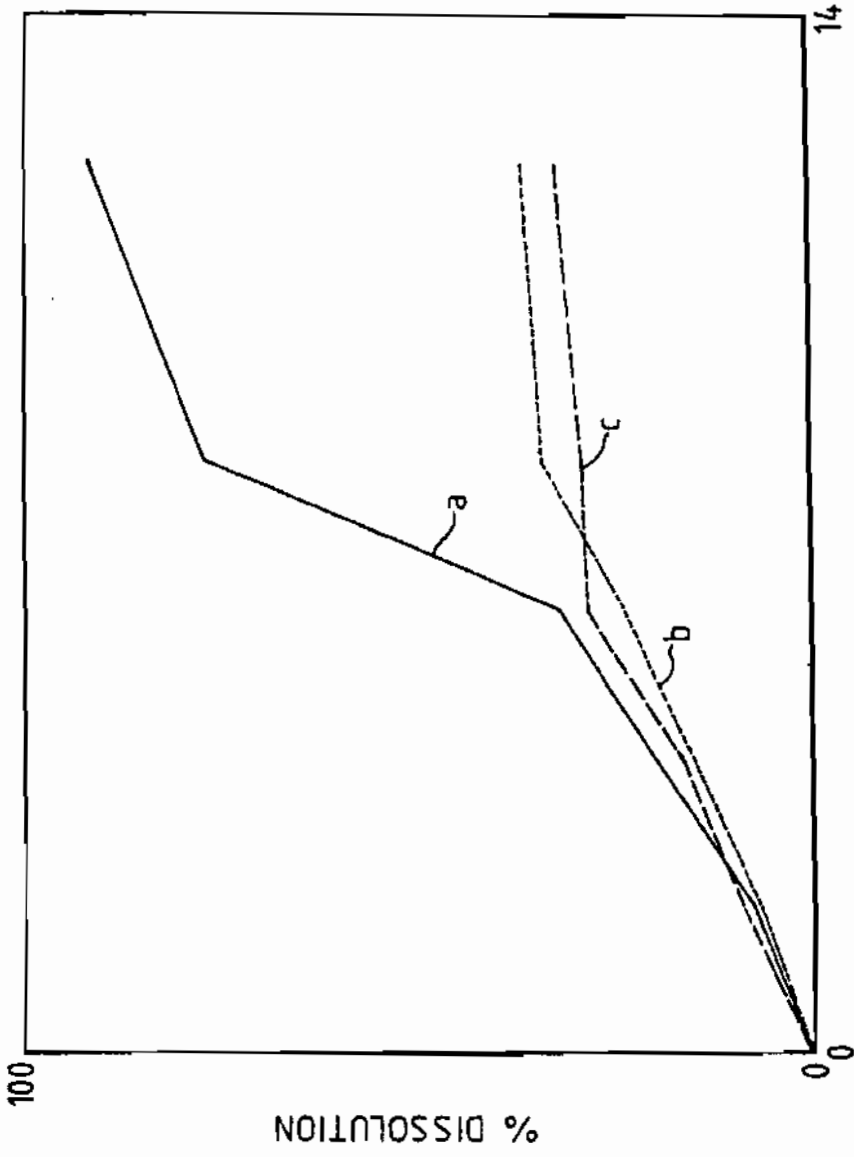

FIG. 6.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 98 10 5888

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,X	EP 0 149 920 A (ELAN) 31 July 1985 * the whole document *	1-12	A61K31/55 A61K9/50
A		13-15	
Y	EP 0 077 956 A (TANABE) 4 May 1983 * page 11 * * page 21 - page 22 * * claims *	1-12	
Y	EP 0 214 735 A (EUROCELTIQUE) 18 March 1987 * claims 1-6 *	1-12	
A	EP 0 122 077 A (ELAN) 17 October 1984 * claims *	1-15	
A	EP 0 123 470 A (ELAN) 31 October 1984 * claims *	1-15	
A	EP 0 156 077 A (ELAN) 2 October 1985 * claims *	1-15	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A	EP 0 225 085 A (ELAN) 10 June 1987 * claims *	1-15	A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	14 May 1998	Alvarez Alvarez, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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EPO FORM 1503 03.82 (P04C01)

EXHIBIT C

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(54) Title: EXTENDED-RELEASE FORM OF DILTIAZEM

(57) Abstract

An extended-release galenical form of Diltiazem or a pharmaceutically acceptable salt thereof, which comprises beads containing said Diltiazem or a pharmaceutically acceptable salt thereof as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant.

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EXTENDED RELEASE FORM OF DILTIAZEM

FIELD OF INVENTION

The present invention relates to an extended release form of Diltiazem, a process for the manufacture thereof and pharmaceutical compositions containing the same.

BACKGROUND OF THE INVENTION

Diltiazem hydrochloride is used in medicine principally for its calcium channel blocking properties, and, therefore, finds application in the treatment of angina pectoris and hypertension, either alone or in combination with other medications.

Although the mechanism for calcium channel blocking is not completely understood, calcium ion entry is believed to be inhibited through select voltage, with the sensitive areas termed "slow channels", across cell membranes. By reducing intracellular calcium concentration in cardiac and vascular smooth muscle cells, coronary arteries, peripheral arteries and arterioles are dilated and heart rate may be reduced. Also, myocardial contractibility may be decreased and atrioventricular nodal conduction may be slowed. The activity of diltiazem in humans is directly related to its blood or plasma concentration.

For illnesses which require continuous and constant control, such as hypertension and angina pectoris, Diltiazem must be administered every 6 to 8 hours, as it has a very short half-life in blood of only about 3 to 4 hours. However, such frequent administration times render the treatment very annoying or even impossible to effect, particularly during the night. Further, after each administration of an immediate-release galenic form of Diltiazem, which generally is necessary four times per day, a succession of rapidly increasing and decreasing plasmatic Diltiazem concentrations are established. Thus, the organism being treated and the target organ, more particularly the heart, are alternatively subjected to overdoses and to underdoses of medicine.

In order to alleviate these drawbacks, a first galenic form of sustained-release Diltiazem known under the

trade name CARDIZEM SR® was developed and presented in the form of "erodible pellets", U.S. Patent 4,721,619. Although this form affords a reduction in peak concentration and in the number of daily intakes from 4 to 2, it does not eliminate high Diltiazem blood concentration between successive medication intakes. Hence, the patient is still obliged to take the medication twice daily. The products as described in U.S. 4,721,619 are prepared by a building up process which requires, as described therein, between 50 and 200 layers so as to obtain a core which, thereafter, requires between 20 and 40 layers of coating so as to obtain the membrane. Moreover, the solvent of the polymer solution used to make the membrane is constituted by organic solvents, such as isopropanol, methanol, acetone, and methylene chloride, which are dangerous to use due to their flammability and/or toxicity. Such solvents are also environmentally hazardous. Particular care must be taken to avoid any traces of solvent in the final product because these solvents are toxic and are unsuitable in the product which is administered orally.

Thus, a need continues to exist for a multiple unit extended-release diltiazem hydrochloride galenical form which need be administered only once daily, and from which blood Diltiazem concentrations are not effected by the concomitant intake of food, and, further, which can be made by a process not using organic solvents.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide galenic forms of Diltiazem with extended release of the active substance.

It is also an object of this invention to provide galenic forms of Diltiazem having excellent bioavailability while avoiding plasmatic concentration peaks.

The above objects and others which will become more apparent in view of the following disclosure are provided by an extended-release galenical form of a pharmaceutically acceptable salt of Diltiazem, which

comprises beads containing the pharmaceutically acceptable salt of Diltiazem as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

Thus, according to one embodiment of the invention an extended-release galenical composition comprises beads comprising:

a) an effective amount of said one or more Diltiazem salts as an active ingredient, and

b) a wetting agent, wherein said wetting agent comprises a sugar, C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof,

wherein said beads are coated with a microporous membrane of an aqueous dispersion of a water-soluble or water-dispersible polymer or copolymer, for example a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically acceptable adjuvant.

According to another embodiment a pharmaceutical composition is provided, comprising in capsule form an effective amount of one or more pharmaceutically acceptable salts of Diltiazem, and a wetting agent, wherein said wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof,

wherein said beads are coated with a microporous membrane of an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a

pharmaceutically acceptable adjuvant, and one or more other pharmaceutically active ingredients which are pharmaceutically compatible with said one or more Diltiazem salts.

According to another aspect of the invention a method of treating angina pectoris or hypertension or both in a mammal is provided which comprises administering to said mammal an effective amount of an extended-release galenical composition of Diltiazem or a pharmaceutically acceptable salt thereof and a wetting agent in the form of beads, wherein the wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof,

wherein the beads are coated with a microporous membrane of for example an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically acceptable adjuvant.

According to another aspect of the invention, the extended-release galenical formulation is adapted to release Diltiazem in 900 ml of water when USP XXII, apparatus no. 2 is used at 100 rpm, at a rate in the order of:

between about 5% and about 20% after 2 hours, for example 9% after two hours (in one embodiment with 5% after 1 hour);

between about 20% and about 50% after four hours, for example 33-34% after four hours;

between about 30% and about 70% after six hours, for example 54% after 6 hours; and

between about 50% and about 90% after 8 hours, for example, between about 62% and about 82% after 8 hours.

Thus, according to another aspect of the invention an extended-release galenical composition is provided comprising beads containing:

a) an effective amount of said one or more Diltiazem salts as an active ingredient, and

b) a wetting agent, wherein the wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, alcohol-polyglycide ester or lecithins or any combination thereof,

wherein said beads are coated with a microporous membrane of for example an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically acceptable adjuvant, wherein the membrane is adapted to release Diltiazem, in 900 ml of water when USP XXII, apparatus no. 2 is used at 100 rpm, at a rate on the order of:

9% after 2 hours,
33% after 4 hours,
54% after 6 hours, and
between 62% and 83% after 8 hours.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be illustrated with respect to the following drawings illustrating embodiments of the invention in which:

Figure 1 illustrates the effect of the present invention in gradually releasing Diltiazem in a relatively uniform manner over a period of about one day after the 8th once daily administration in comparison with the effect of a conventional product after the 8th day of administration twice daily.

Figure 2 illustrates in the solid curve, the mean plasma levels obtained when the product of the present invention is taken without food. The dotted curve represents mean plasma levels obtained when the product is taken with food.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

Diltiazem or (2S-cis)-3-(Acetyloxy)-5-[2-(dimethyl-amino)ethyl]-2,3-dihydro-2, (4-methoxyphenyl)-1,5-benzothiazepin-4(5H) has been known for more that 20 years. The synthesis thereof is described in German patent 1,805,714, corresponding to U.S. patent 3,562,257.

The present invention relates to novel galenic forms of Diltiazem being characterized by having an extended-release of the active substance. These galenic forms afford excellent bioavailability while avoiding plasmatic concentration peaks, so that it is now possible to maintain diltiazem plasmatic concentration in a desired, effective range while simplifying the administration of the medicine to only once daily.

According to the present invention, the Diltiazem extended-release galenic forms are substantially characterized by the fact that they are constituted by beads containing a pharmaceutically acceptable salt of Diltiazem as an active substance, associated with at least a wetting agent, the beads being covered with a microporous membrane constituted by at least a water-soluble or water-dispersible polymer or copolymer such as a copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, and a pharmacologically acceptable adjuvant.

In accordance with the present invention, any pharmaceutically acceptable salt of Diltiazem may be prepared in extended release form. For example, such salts may include the hydrochloride, sulfate or phosphate salts. However, they may also include the acetate, citrate or lactate salts, for example. It is preferred, however, that the hydrochloride salt be used.

In more detail, the microporous membrane, whereof the Diltiazem-containing microgranules are covered, is constituted by a mixture of a water-soluble and/or water-dispersible copolymer, including at least one adjuvant which may be the active substance. These galenic forms afford

excellent bioavailability while avoiding plasmatic concentrations peaks, so that it is now possible to maintain diltiazem plasmatic concentrations in a desired, effective range while simplifying the administration of the medicine to only once daily.

According to the the present invention, the Diltiazem extended release galenic forms are substantially characterized by the fact that they are constituted by beads containing a pharmaceutically acceptable salt of Diltiazem as an active substance, associated with at least a wetting agent, the beads being covered with a microporous membrane constituted by at least a water-soluble or water-dispersible polymer or copolymer such as a copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, and a pharmacologically acceptable adjuvant.

In accordance with the present invention, any pharmaceutically acceptable salt of Diltiazem may be prepared in extended release form. For example, such salts may include the hydrochloride, sulfate or phosphate salts. However, they may also include the acetate, citrate or lactate salts, for example. It is preferred, however, that the hydrochloride salt be used.

In more detail, the microporous membrane, whereof the Diltiazem-containing microgranules are covered, is constituted by a mixture of a water-soluble and/or water-dispersible copolymer, including at least one adjuvant which may be plastifying agents, pigments, fillers, wetting agent lubricants and antifoam agents.

The active substance-containing beads are presented in form of spherules the diameter of which is between about 0.05 mm and 3 mm, preferably between about 0.1 mm and 2 mm.

Among the wetting agents associated with the Diltiazem or salt thereof in the beads, the following compounds may more particularly be exemplified:

sugars, for example saccharose, mannitol, sorbitol and lactose;

lecithins;

C_{12} to C_{20} fatty acid esters of saccharose, commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.);

xylose esters or xylites;

polyoxyethylenic glycerides;

esters of fatty acids and polyoxyethylene (Brijs, Renex and Eumulgines, Henkel, RFA);

sorbitan fatty acid esters (Span, Atlas, U.S.A.);

polyglycides-glycerides and polyglycides-alcohols esters (Gelucires, Gattefosse, France).

In addition to at least one of the above-named wetting agents, the beads may contain excipients or carriers, such as:

Microcrystalline celluloses, such as Avicel products (FMC, U.S.A.); methylcelluloses, carboxymethylcelluloses, hydroxyethylcelluloses (Natrosol, Hercules, U.S.A.), hydroxypropyl celluloses (Klucels, Hercules, U.S.A.); and starches.

Among the water-soluble and/or dispersible film-forming polymers or copolymers constituting the microporous membrane, may be mentioned particularly polyacrylates and polymethacrylates of the Eudragit type, such as Eudragit E30D, L30D, RS - 30 D of Röhm Pharm (RFA), ethylcelluloses, such as Ethocels of DOW, U.S.A. and such as AquaCoat of FMC, U.S.A., Hydroxypropyl cellulose and hydroxypropyl-methylcellulose and their derivations.

These polymers or copolymers may be associated into the microporous membrane with at least one adjuvant as exemplified by the following:

plastifying agents, such as triacetin, dibutylphthalate, dibutylsebacate, citric acid esters, polyethyleneglycols, polypropyleneglycols and polyvinylpyrrolidone;

pigments, such as iron oxides and titanium oxide;

fillers, such as lactose and sucrose;

wetting agents, such as surfactive agents of the Span and Tween types, namely partial esters of fatty acids (lauric, palmitic, stearic and oleic acids) and anhydrides of hexitols derived from sorbitol possibly containing polyoxyethylenic chains, preferably surfactive agents of the Tween type, namely Tween 80, as well as polyethyleneglycols;

lubricants, such as magnesium stearate and talc;

antifoaming agents, such as silicone oil.

In addition to the polymer or copolymer, the microporous membrane contains, preferably, talc and/or magnesium stearate as a lubricant, polyvinylpyrrolidone as a plastifying agent, titanium dioxide as a pigment, Tween 80 as an emulsifier, and silicone oil as an antifoaming agent.

Generally, the thickness of the microporous membrane is expressed by the percentage of the coating applied to the uncoated beads.

The weight of the microporous membranes may be 2 to 35%, preferably, 5 to 22%, of the weight of said microgranules. These beads may contain the Diltiazem salt in an amount of 20 to 95% by weight, preferably 30 to 85% by weight. The microporous membrane may contain 5 to 95% and, preferably, 30 to 90% of polymers, polymer mixture or copolymers.

The invention relates also to a medicine containing Diltiazem or salt thereof for extended release, the medicine being constituted by beads containing the Diltiazem or salt, such as the hydrochloride, and at least a wetting agent, coated with at least one polymer-based microporous membrane, the coated beads being contained in capsules, little bags or dosage dispensers.

The present invention relates also to a process for obtaining novel forms of a Diltiazem or salt thereof having extended-release in the gastro-intestinal tractus, said process entailing preparing beads and coating the same with a single microporous membrane.

The beads of the Diltiazem or salt thereof may be prepared using a conventional technique. A first technique consists in mixing the Diltiazem or salt thereof with the wetting agent(s) in a melted or finely divided form, or in solution, in the presence of a solvent, such as water, so as to obtain an extrudable paste or plastic mass. Said paste is thereafter extruded in an extruder and then rendered spherical. Several extruder types are usable, for example the extruder for ALEXANDER WERK (RFA) or the apparatus called X-truder of FUJI-PAUDAL (Japan). For obtaining microspheres or beads from the extruded product provided in the form of spaghetti, an apparatus called "spheronizer" (CALEVA Great-Britain) or MARUMERIZER (FUJIU-PAUDAL Japan) type is used.

Another conventional technique for obtaining beads consists in spraying and/or dusting cores obtained through agglomeration of the Diltiazem or salt thereof, such as the chlorohydrate, contingently mixed to at least a wetting agent, with a dispersion or solution of at least one wetting agent, for example in a known pilling turbine or in a granulating apparatus, such as the CF granulator system of FREUND INDUSTRIAL CO. (Japan), or in a known planetary granulator such as the collette (Belgium) type.

The obtained beads are dried by any means, for example in an oven or by means of a gas in a fluidized bed.

Finally, said beads are calibrated to the necessary diameter by passage through appropriate screens.

A pasty or plastic mixture, appropriate to be granulated by means of any one of the above described techniques, may contain the following weight proportions of the Diltiazem or salt thereof, wetting agents and carriers or excipients:

20 to 85%; Diltiazem hydrochloride
2 to 20% sucroesters WE 15 (wetting agent);
5 to 25% Avicel PH 101 (microcrystalline cellulose of FMC, U.S.A.);
2 TO 10% Methocel E 5 (hydroxypropyl-

methylcellulose of DOW, U.S.A.);
1 to 15% polyvinylpyrrolidone and
5 to 40% distilled water.

Said microporous membrane may be applied onto said beads by pulverizing an aqueous solution or dispersion of at least one of the above-named polymers and at least one of the above-mentioned adjuvants onto said beads. This pulverization may be carried out by spray-gunning or by pulverizing the above-named dispersion into a turbine or fluidized bed.

Generally, the present extended release form composition of Diltiazem salt is administered orally. The dosage amount is subject to the response of the individual patient; however, in general, from about 120 mg to about 480 mg per day of Diltiazem salt is administered per day per patient in total.

Additionally, the extended release form composition of the present invention may include other pharmaceutically active ingredients than the Diltiazem salt, provided that the other active ingredient is not pharmaceutically incompatible with the Diltiazem salt.

For example, other pharmaceutically active ingredients, such as β-adrenoceptor blocking agents or diuretics may be used in the present compositions. However, these are only examples and are not intended to be limitative.

As examples of β-adrenoceptor blocking agents, drugs such as Propranolol, Atenolol, Labetalol, Prindolol or Sotalol may be used, for example.

As examples of diuretic agents, drugs such as Hydrochlorothiazide, Furosemide, Ethacrynic Acid or Chlorothiazide may be used, for example.

Further, the additional associated drugs may be present in extended-release form also, if desired; however, they need not be.

The present invention will now be further illustrated by reference to certain examples which are

provided solely for purposes of illustration and are not intended to be limitative.

According to an illustrative embodiment of the present invention, said microporous membrane may be obtained, starting from an aqueous dispersion which contains by weight:

10 to 70 Eudragit E30D (polymer)
0.5 to 15% talc (lubricant)
0.5 to 15% Titanium dioxide (lubricant)
0.5 to 15% Magnesium stearate (lubricant)
0.5 to 15% polyvinylpyrrolidone (plastifying agent)
0.01 to 2% silicone oil (antifoaming agent);
0.05 to 5% polysorbate 80 (wetting agent)
10 to 70% water (carrier)

EXAMPLES

The present invention will now be further illustrated by reference to certain examples, which are provided solely for purposes of illustration and are not intended to be limitative. In particular, examples are provided for Diltiazem Hydrochloride extended-release galenic forms, a process for preparing the same, therapeutic applications thereof and pharmacokinetic controls using the present galenic forms.

Example 1 - beads manufacture

Diltiazem hydrochloride	1120 g
Lactose	119 g
Microcrystalline cellulose (Avicel pH 101)	140 g
Povidone K. 30	21 g

After introducing the powders into a planetary mixer and granulating with water, the obtained plastic mass is extruded through a cylinder with 1 mm diameter holes (Alexanderwork). The small cylinders are rounded, so as to

obtain beads, by means of a spheronizer. After drying at 60°C for 12 hours, the beads are sifted and the fraction with size comprised between 0.7 mm and 1.4 mm are retained. 1,179 g of beads were obtained yield (84%).

Example 2

Diltiazem Hydrochloride	560 g
Crodesta F 160	59.5 g
Microcrystalline cellulose (Avicel pH 101)	70 g
Povidone K 30	10.5 g

The ingredients are introduced in a planetary mixer and dry mixed for approximately 15 minutes. Thereafter, 100 ml water USP is added and the mixing is pursued for 10 minutes more until a plastic mass is obtained. This mass is then extruded through a Fuji Paudal extruder equipped with a 1 mm screen so as to obtain "spaghetties". A spheronizer type caleva is used so as to transform the extruded product into beads. After drying for 12 hours on trays in an oven at 60°C, the beads are sieved so as to eliminate the ones with a size larger than 1.4 mm and with a size smaller that 0.7 mm.

The amount of beads obtained with size comprised between 0.7 mm and 1.4 mm was 639.1 g (yield 91.3%).

Example 3

Beads prepared in Example 1 were coated in a STREA-1 (Aeromatic) fluidized bed using the "Top spraying" technique. 440 g of coating suspension of the following composition was applied on 500 g of beads. Thereafter, the coated beads were dried at 50°C during 16 hours.

Coating suspension composition:	
Magnesium stearate	12.5 g
Titanium dioxide	5.0 g
Povidone k 30	5.0 g
Eudragit NE30D	620.0 g
Talc USP	17.5 g
water	338.0 g
Simethicone	1.0 g
Tween 80	0.8 g

"In vitro" dissolutions were obtained using the apparatus #2 as described in the United States Pharmacopeia. The 900 ml dissolution medium consisted of a phosphate butter of 5.8 pH and a revolution speed of 100 rpm.

elapsed time [h]	percent dissolved [%]
1	5
4	34
8	62
12	84

Example 4

The beads, as in Example 2, were coated using a fluidized bed coater equipped with "wurster" system. 8 kg of uncoated beads were introduced in an Aeromatic Aerocoater and 2.77 kg of the following coating suspension was applied at a rate of 30 - 35 g per minute. Thereafter, the coated beads were dried for 15 hours at 45°C.

Coating suspension:		
Magnesium stearate	0.636	kg
Talc	0.636	kg
Titanium dioxide	0.0909	kg
Hydroxypropylmethylcellulose	0.200	kg
Polysorbate 80 NF	0.007	kg
Simethicone c emulsion	0.018	kg

Eudragit NE 30 D	12.4	kg
purified water	6.7	kg

Dissolution "in vitro"

The results were obtained using the same equipment as in Example 3. The dissolution medium was composed of 900 ml of water and the temperature was maintained at 37 ± 0.5°C

elapsed time [h]	percent dissolved [%]
2	9
4	33
6	54
8	82

Pharmacokinetical results

The new galenic form of Example 4 was the object of a pharmacokinetical study in comparison with a form in accordance to the prior art as described in U.S. Patent 4,721,619 (Cardizen SR®). Therefore, 6 healthy subjects received successively in a random order 300 mg of each of the 2 products. The product of Example 4 was administered at a dose of 300 mg once daily, while the product on the market was administered twice daily at a dose of 150 mg (300 mg daily total dose) for 7 days. On each of the eight days, 11 samples of blood were withdrawn when the product of Example 4 was administered and 15 blood samples were withdrawn after the Cardizen SR® administration. Diltiazem plasma levels were assayed using a specific high pressure liquid chromatographic method. Figure 1 shows the results obtained: the continuous line represents the Diltiazem plasma levels obtained with the product of Example 4 and the broken line, the Diltiazem plasma levels of Cardizen SR®.

Figure 1

Pharmacokinetical parameters:

	Units	Example 4	Cardizen SR®
Area under the curve [0-24h]	mg.h/ml	2782 ± 1037	2864 ± 1222
Maximal concentration	mg/ml	116.3 ± 54.1	192.7 ± 85.3
Time of maximum concentration	h	8.0 ± 1.8	5.2 ± 2.8
Fluctuation	%	85.7 ± 25.7	109.5 ± 25
Time during the concentration is above 75% of the maximum concentration	h	9.8 ± 2.3	6.7 ± 3.7

From these results, the following conclusion can be drawn:

Firstly, Fig. 1 shows that the Diltiazem plasma levels obtained after a once daily administration of one of the products of the present invention are comparable to the ones obtained after a twice daily administration of the product of the previous art.

Secondly, the bioavailability expressed by the areas under the curve of the 2 products is equivalent (no statistical detectable difference).

Thirdly, the maximal concentration and the fluctuations obtained after a once daily administration of the product of the present invention is lower than the one obtained with Cardizen SR® after a twice daily administration.

Fourthly, the time that the concentration is above 75% of the maximum concentration is 46% longer after the once daily administration of the product of the present invention than with the product of the previous art when given twice daily.

Food effect study

The product of Example 4 was given to 24 healthy volunteers and the bioavailability was measured after a single oral dose of 300 mg given with and without food.

The clinical trial was conducted as an open, single dose, randomized, cross-over study. Blood samples were obtained before and up until 36 hours after the administration. The experiment was repeated in the same subjects with the other treatment during an interval of 7 days. The plasma concentration of Diltiazem was determined in all available samples using an HPLC method. Pharmacokinetics parameters were derived from the individual plasma concentration versus time profiles and statistically compared for treatment differences and assessment of bioequivalence. Figure 2 curves show the mean plasma levels obtained when the product is taken without food and the dotted curve, the mean plasma levels obtained when the product is taken with food.

Figure 2

Pharmacokinetics parameter - product of Example 4

	Units	Fasting	Food
Area under the curve (total)	mg.h/ml	1988 ± 119	1925 ± 109
Mean residence time	h	21.3 ± 0.7	19.9 ± 0.9
K_a	h^{-1}	0.283 + 0.024	0.300 + 0.027
Maximum concentration	mg/ml	100 ± 4.8	112 ± 5.9

No statistical difference was detectable. The product of Example 4 given with food is bioequivalent to the administration without food to within less than 20%, regarding the area under the curve, mean residence time and maximum concentration. The larger interval obtained for K_a

was due to the higher variability of this parameter, the difference between the treatment means remaining small (6.%).

From all the results, it appears clearly that the product of the present invention can be administered once a day and that the plasma concentration variations are lower than the ones obtained with the conventional product given twice a day.

Having described the present invention, it will now be apparent to one skilled in the art that many changes and modifications may be made to the above-described embodiments while remaining within the spirit and the scope of the present invention.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. An extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which comprises beads containing an effective amount of said one or more Diltiazem salts as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

2. The extended-release galenical composition of Claim 1, wherein said salt is the hydrochloride salt.

3. The extended-release galenical composition of Claim 1, wherein said water-soluble or water-dispersible polymer is a polymer of acrylic acid methyl ester and acrylic acid ethyl ester or a copolymer of both.

4. The extended-release galenical composition of Claim 1, wherein said wetting agent comprises a sugar, C_{12} to C_{20} fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, glyceride-polyglycides, alcohol-polyglycide esters or lecithins or any combination thereof.

5. The extended-release galenical composition of Claim 1, wherein the weight of the microporous membrane is about 4 to 35% by wt. of that of the uncoated beads.

6. A pharmaceutical composition containing an extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which comprises:

a) beads containing an effective amount of one or more pharmaceutically acceptable salts of Diltiazem and a wetting agent, said beads being coated with a microporous membrane containing at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant, and

b) one or more other pharmaceutically active ingredients which pharmaceutically active ingredients are pharmaceutically compatible with said one or more Diltiazem salts.

7. The pharmaceutical composition of Claim 6, wherein said one or more other pharmaceutically active ingredients comprises β-adrenoceptor or diuretic compounds or compositions containing the same.

8. A method for treating angina pectoris or hypertension or both in a mammal, which comprises administering to said mammal an effective amount of an extended-release galenical composition of Diltiazem or a pharmaceutically acceptable salt thereof in the form of beads, said beads being coated with a microporous membrane containing at least a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

9. The method of Claim 8, wherein said administration is orally and once per day.

10. The method of Claim 8, wherein said mammal is a human.

11. The method of Claim 9, wherein from about 120 mg to about 480 mg of said one or more Diltiazem salts in total are administered per day.

12. An extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which comprises beads, said beads comprising:

a) an effective amount of said one or more Diltiazem salts as an active ingredient, and

b) a wetting agent, wherein said wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof,

wherein said beads are coated with a microporous membrane of at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant.

13. The extended-release galenical composition of Claim 12, wherein said salt is the hydrochloride salt.

14. The extended-release galenical composition of Claim 12, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

15. The extended-release galenical composition of Claim 12, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

16. The extended-release galenical composition of Claim 12, wherein the water-soluble or water-dispersible polymer or copolymer comprises an aqueous dispersion or a neutral copolymer or ethyl acrylate and methyl methacrylate.

17. A pharmaceutical composition comprising an extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which

comprises in capsule form,

beads comprising an effective amount of one or more pharmaceutically-acceptable salts of Diltiazem, and a wetting agent, wherein said wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant, and

one or more other pharmaceutically active ingredients which are pharmaceutically compatible with said one or more Diltiazem salts.

18. The pharmaceutical composition of Claim 17, wherein said one or more other pharmaceutically active ingredients comprises β-adrenoceptor or diuretic compounds or compositions containing the same.

19. The pharmaceutical composition of Claim 17, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

20. The pharmaceutical composition of Claim 17, wherein said salt is the hydrochloride salt.

21. The pharmaceutical composition of Claim 17, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

22. A method for treating angina pectoris or hypertension or both in a mammal, which comprises administering to said mammal an effective amount of an

extended-release galenical composition of Diltiazem or a pharmaceutically acceptable salt thereof in the form of beads and a wetting agent, wherein the wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof, wherein the beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant.

23. The method of Claim 22, wherein said administration is orally and once per day.

24. The method of Claim 22, wherein said mammal is a human.

25. The method of Claim 23, wherein from about 120 mg to about 480 mg of said one of more Diltiazem salts are administered in total per day.

26. The method of Claim 22, wherein said salt is the hydrochloride salt.

27. An extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which comprises beads containing:

a) an effective amount of said one or more Diltiazem salts as an active ingredient, and

b) a wetting agent, wherein the wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of

polyoxyethylene sorbitan, a glyceride-polyglycide, alcohol-polyglycide ester or lecithins or any combination thereof, wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant, wherein the membrane is adapted to release Diltiazem, in 900 ml of water when USP XXII, apparatus no. 2 is used at 100 rpm, at a rate on the order of:

9% after 2 hours,
33% after 4 hours,
54% after 6 hours, and
between 62% and 82% after 8 hours.

28. The extended-release galenical composition of Claim 27, wherein said salt is the hydrochloride salt.

29. The extended-release galenical composition of Claim 27, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

30. The extended-release galenical composition of Claim 29, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

31. An extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which comprises beads containing:

a) an effective amount of said one or more Diltiazem salts as an active ingredient, and

b) a wetting agent, wherein the wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, alcohol-polyglycide ester or lecithins or any combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically acceptable adjuvant, wherein the membrane is adapted to release Diltiazem, in 900 ml of water when USP XXII, apparatus no 2. is used at 100 rpm, at a rate on the order of:

between 5% and 20% after 2 hours,
between 20% and 50% after 4 hours,
between 30% and 70% after 6 hours, and
between 50% and 90% after 8 hours.

32. The extended-release galenical composition of Claim 31, wherein said salt is the hydrochloride salt.

33. The extended-release galenical composition of Claim 31, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

34. The extended-release galenical composition of Claim 33, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

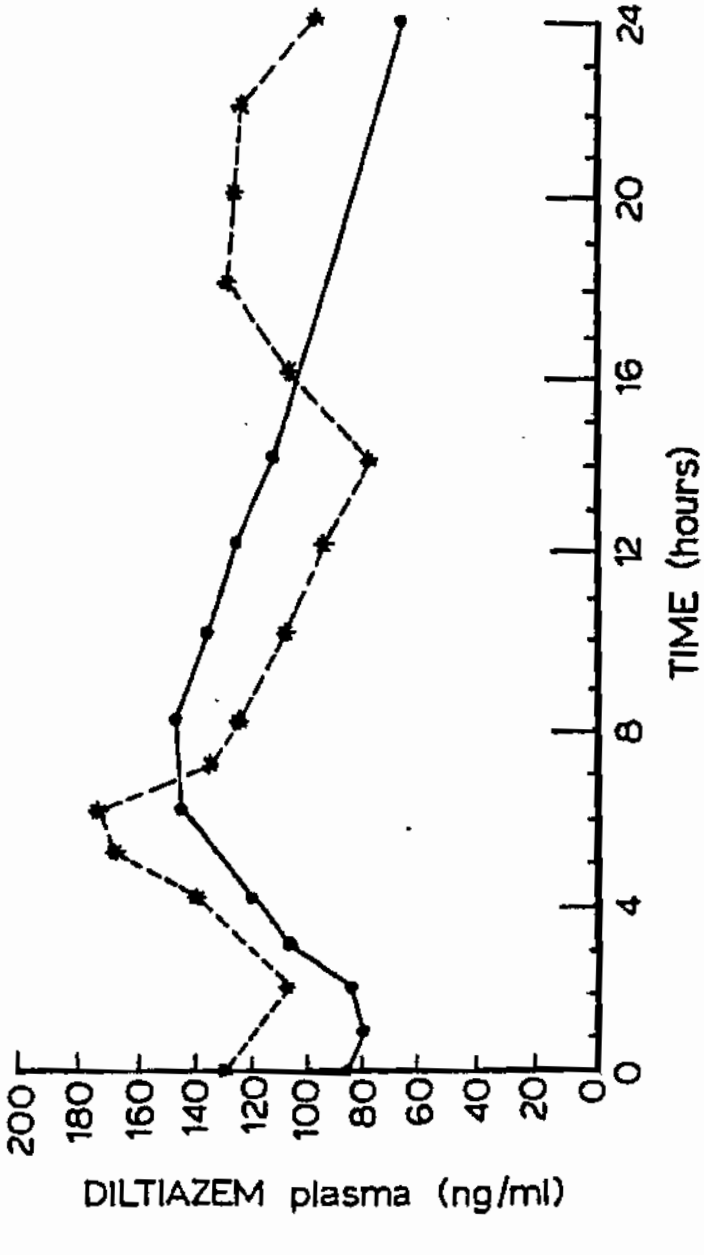

200
180
160
140
120
100
80
60
40
20
0
DILTIAZEM plasma (ng/ml)
0
4
8
12
16
20
24
TIME (hours)

FIG.1.

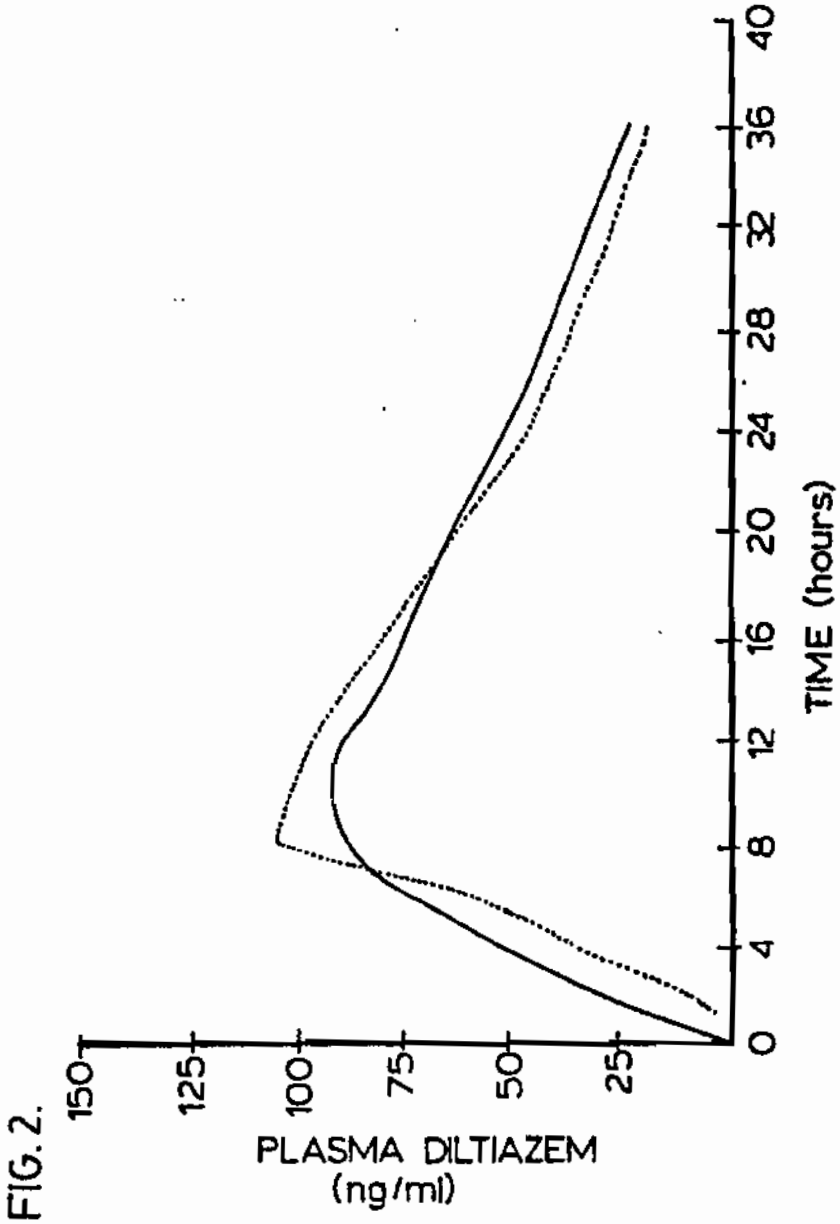

TIME (hours)
0
4
8
12
16
20
24
28
32
36
40
PLASMA DILTIAZEM
(ng/ml)
150
125
100
75
50
25

FIG. 2.

INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 92/00290

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/55 A 61 K 9/52 A 61 K 9/54

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0373417 (SCHERING) 20 June 1990, see the claims; page 3, lines 25-53; page 4, lines 21-32	1-3,12-13,16-17,20,27-28,31-32
A	EP,A,0340105 (SANOFI) 2 November 1989, see the claims; column 2, lines 9-31; column 3, lines 4-23,46-53	1-3,12-13,16-17,20,27-28,31-32
A	EP,A,0322277 (SYNTHELABO) 28 June 1989, see the claims; column 1, lines 23-52; column 2, lines 23-29	1-3,12-13,16-17,20,27-28,31-32

-/-

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
01-09-1992	21. 09. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0149920 (ELAN) 31 July 1985, see the claims; page 4, lines 26-35 (cited in the application)	1-4

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. CA 9200290 SA 61640

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 16/09/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0373417	20-06-90	AU-A-	4664889	26-06-90
		CA-A-	2004565	31-05-90
		WO-A-	9006107	14-06-90
EP-A- 0340105	02-11-89	FR-A-	2630647	03-11-89
		AU-B-	614056	15-08-91
		AU-A-	3336389	02-11-89
		DE-U-	6890090	09-04-92
		JP-A-	1313431	18-12-89
EP-A- 0322277	28-06-89	FR-A-	2624732	23-06-89
		AU-A-	2707788	22-06-89
		DE-A-	3868037	05-03-92
		JP-A-	2000202	05-01-90
		US-A-	5112621	12-05-92
EP-A- 0149920	31-07-85	BE-A-	901359	16-04-85
		CH-A-	662507	15-10-87
		DE-A-	3485023	10-10-91
		JP-A-	60156617	16-08-85
		US-A-	4891230	02-01-90
		US-A-	4917899	17-04-90
		US-A-	4894240	16-01-90
		US-A-	4721619	26-01-88

EXHIBIT D

1615

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 09/567,451	Confirmation No.	: 5428
First Named Inventor	: Kenneth ALBERT		
Filed	: May 8, 2000		
TC/A.U.	: 1615		
Examiner	: Susan Tran		
Docket No.	: 100338.55781US		
Customer No.	: 23911		
Title	: Chronotherapeutic Diltiazem Formulations and the Administration Thereof		

REPLY, AMENDMENTS AND SUBMISSION OF AFFIDAVIT BY EDITH MATHIOWITZ, PH.D. AND EXHIBITS

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The following amendments and remarks are presented further the Request for Continued Examination filed on January 26, 2005.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 36 of this paper.

Amendments to the Claims:

The listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims

Claim 1 (currently amended): An orally administrable ~~a~~ controlled-release ~~Galenical preparation of~~ composition comprising a pharmaceutically acceptable form of diltiazem selected from the group consisting of diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours the dosage comprising at least one bead comprising a core and at least one coating, the at least one bead being formulated in an oral dosage form containing from about 120 mg to about 540 mg ~~(as desired)~~ of the form of diltiazem, the diltiazem in the core of each bead associated with excipients, the at least one coating covering the core comprising a water swellable and diffusible coating which permits hydration of the core by gastrointestinal fluids, the water swellable and diffusible coating comprising the following constituents: (i) at least one lubricant and/or at least one hydrophilic polymer and (ii) further comprising as an essential constituent at least one water insoluble swellable neutral copolymer, wherein said constituents (i) and (ii) which comprise said coating, the ratios thereof, and the amount of said coating are formulated such that said orally administrable composition: ~~and a neutral copolymer, the at least one bead providing controlled (sustained) release of the form Diltiazem in oral sustained release dosage form in which the form of Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans~~

A) in vitro exhibits the following in vitro release characteristics;

(i) releases the diltiazem or a pharmaceutically acceptable salt thereof into a aqueous medium at the following rates when measured using the method of United States Pharmacopoieia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;

(b) between about 7% and about 35% after 4 hours;

(c) between about 30% and about 58% after 8 hours;

(d) between about 55% and about 80% after 14 hours;

(e) in excess of about 75% after 24 hours;

and/or (ii) releases the diltiazem or pharmaceutically acceptable salt thereof into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoieia No. XXIII at 100 rpm in 900 ml of the buffered medium:

(a) between about 1% and about 25% after 2 hours;

(b) between about 7% and about 45% after 4 hours;

(c) between about 30% and about 68% after 8 hours;

(e) in excess of about 75% after 24 hours;

and

further wherein said orally administrable composition having said in vitro release characteristics results in a composition that:

B) when orally given to humans exhibits the following properties:

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with or without food according to the same FDA guidelines or criteria;

and

(iii) provides a Cmax of diltiazem in the blood at between about 10 hours and 15 hours after administration.

Claim 2 (currently amended): The controlled release ~~Galenical~~ preparation of claim 1 wherein the water insoluble swellable neutral copolymer is selected from the group consisting of

(i) a water-, acid-, and base-insoluble polymer of a neutral acrylic polymer,

(ii) a neutral acrylic copolymer of ethyl acrylate and methyl methacrylate, and

(iii) a neutral copolymer without any functional groups that form water insoluble films and the lubricant is selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative and/or the hydrophilic polymer is selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof.

Claim 3 (deleted)

Claim 4 (deleted)

Claim 5 (currently amended): The controlled-release ~~Galenical~~ preparation of claim 1 ~~2~~ in which the form of diltiazem is adapted to be control released after administration of the preparation over a period of time and is more preferably ~~being~~ adapted to release the diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours.

Claim 6 (previously amended): The preparation of claim 4 wherein the Cmax of diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

Claim 7 (previously amended): The preparation of claim 1, 2, ~~4,~~ 5 or 6 wherein the form of diltiazem is Diltiazem HCl.

Claim 8 (previously amended): The preparation of claim 6 wherein the preparation is a diffusion controlled preparation.

Claim 9 (previously amended): The preparation of claim 5 wherein the preparation releases the diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

Claim 10 (previously amended): The preparation of claim 9 in capsule form.

Claim 11 (previously amended): The preparation of claim 9 in tablet form.

Claim 12 (previously amended): The preparation of claim 9 wherein the preparation comprises a plurality of microgranules, each microgranule

comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

Claim 13 (original): The preparation of claim 12 wherein the diltiazem is mixed (in whole or in part) with the wetting agent.

Claim 14 (previously amended): The preparation of claim 13 wherein the wetting agent assists to maintain the solubility of the diltiazem in each microgranule, ensuring that the solubility of the diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

Claim 15 (previously amended): The preparation of claim 14 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

Claim 16 (previously amended): The preparation of claim 12 wherein the preparation comprises a mixture of the diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

Claim 17 (previously amended): The preparation of claim 16 wherein the membrane comprises a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.

Claim 18 (previously amended): The preparation of claim 17 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

Claim 19 (previously amended): The preparation of claim 13 wherein the diltiazem is mixed with the wetting agent and the membrane comprises an acrylic membrane and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

Claim 20 (previously amended): The preparation of claim 9 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the diltiazem from the preparation.

Claim 21 (previously amended): The preparation of claim 20 wherein the dissolution agent is an organic acid comprising adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid or tartaric acid which permits the diltiazem to dissolve in gastrointestinal fluids even when the microgranules pass into the regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

Claim 22 (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of

diltiazem of claim 1 ~~2~~ to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning, the method comprising administering to a patient in need thereof the preparation in the evening.

Claim 23 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 2 4 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 24 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 5 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 25 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 6 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 26 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 7 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 27 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 8 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 28 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 9 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 29 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 10 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 30 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 11 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 31 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 12 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 32 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 13 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 33 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 14 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 34 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 15 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 35 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 16 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 36 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 17 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 37 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 18 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 38 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 19 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 39 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 20 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 40 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 21 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 41 (currently amended): The preparation of claim 1 ~~5~~ wherein the preparation contains 120 mg of diltiazem.

Claim 42 (currently amended): The preparation of claim 1 ~~5~~ wherein the preparation contains 180 mg of diltiazem.

Claim 43 (currently amended): The preparation of claim 1 ~~5~~ wherein the preparation contains 240 mg of diltiazem.

Claim 44 (currently amended): The preparation of claim 1 ~~5~~ wherein the preparation contains 300 mg of diltiazem.

Claim 45 (currently amended): The preparation of claim 1 ~~5~~ wherein the preparation contains 360 mg of diltiazem.

Claim 46 (currently amended): The preparation of claim 1 ~~5~~ wherein the preparation contains 420 mg of diltiazem.

Claim 47 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 41, 42, 43, 44, 45 or 46 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 48 (previously amended): The preparation of claim 17 wherein the wetting agent is selected from:

sugars;

saccharose, mannitol, sorbitol;

lecithins;

C_{12} to C_{20} fatty acid esters of saccarose;

xylose esters or xylites;

polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene;

sorbitan fatty acid ester;

polyglycides-glycerides and polyglycides-alcohols esters

Metal salts.

Claim 49 (currently amended): The preparation of claim 12 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer selected from the group consisting of ~~such as~~ hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which enables ~~enabling~~ the bead to be hydrated by the introduction of gastrointestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

Claim 50 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 48 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 51 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 49

to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 52 (currently amended): A controlled-release ~~Galenical~~ preparation of pharmaceutically acceptable form of diltiazem according to Claim 1 which comprises the following constituents:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	(Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

Claim 53 (currently amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 52 ~~48~~ to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 54 (previously amended): The preparation of claim 12 in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethyl-cellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

Claim 55 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 54

to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 56 (previously amended): The preparation of claim 12 in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

Claim 57 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 56 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 58 (previously amended): The preparation of claim 12 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of diltiazem during the tablet process, together with suitable excipients and adjuvants.

Claim 59 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 58 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 60 (previously amended): The controlled-release ~~Galenical~~ preparation of claim 2 in which the diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

Claim 61 (original): The preparation of claim 60 wherein the microgranules are in capsule form.

Claim 62 (original): The preparation of claim 60 wherein the microgranules are in tablet form.

Claim 63 (previously amended): The preparation of claim 60 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

Claim 64 (currently amended): A controlled-release ~~Galenical~~ preparation of pharmaceutically acceptable form of diltiazem according to Claim 1, ~~selected from the group consisting of Diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained release dosage form in which the form of Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans~~

~~(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and~~

~~(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:~~ which preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants,

wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	(Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6

(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

Claim 65 (previously amended): The preparation of claim 60 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of diltiazem during the tablet process, together with suitable excipients and adjuvants.

Claim 66 (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 60 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claims 67-109 (cancelled)

Claim 110 (currently amended): A controlled-release ~~Galenical~~ preparation of pharmaceutically acceptable form of diltiazem according to Claim 1, ~~selected from the group consisting of Diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours comprising at least one bead comprising a core and at least one coating, the at least one bead being formulated in an oral dosage form containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients, the at least one coating covering the core comprising a water swellable and diffusable coating which permits hydration of the core by gastrointestinal fluids, the water swellable and diffusable coating comprising at least one lubricant and/or at least one~~

~~hydrophilic polymer and a neutral copolymer, the at least one bead providing controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem~~

~~(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:~~

~~(a) between about 4% and about 8% after 2 hours;~~

~~(b) between about 16% and about 21% after 4 hours;~~

~~(c) between about 44% and about 52% after 8 hours;~~

~~(d) between about 69% and about 76% after 14 hours; and~~

~~(e) and in excess of about 85% after 24 hours;~~

~~and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:~~

~~(a) between about 4% and about 15% after 2 hours;~~

~~(b) between about 16% and about 30% after 4 hours;~~

~~(c) between about 44% and about 62% after 8 hours;~~

~~(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the wetting agent is selected from:~~ wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated

with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the wetting agent is selected from:

sugars;
saccharose, mannitol, sorbitol;
lecithins;
C_{12} to C_{20} fatty acid esters of saccarose;
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene;
sorbitan fatty acid esters;
polyglycides-glycerides and polyglycides-alcohols esters
Metal salts.

Claim 111 (cancelled)

Claim 112 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 110 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 113 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 111 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 114 (currently amended): A controlled-release ~~Galenical~~ preparation of pharmaceutically acceptable form of diltiazem according to Claim 4 ~~selected from the group consisting of Diltiazem and the pharmaceutically acceptable salts~~

~~thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem~~

~~(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:~~

~~(a) between about 4% and about 8% after 2 hours;~~
~~(b) between about 16% and about 21% after 4 hours;~~
~~(c) between about 44% and about 52% after 8 hours;~~
~~(d) between about 69% and about 76% after 14 hours; and~~
~~(e) and in excess of about 85% after 24 hours;~~

~~and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:~~

~~(a) between about 4% and about 15% after 2 hours;~~
~~(b) between about 16% and about 30% after 4 hours;~~
~~(c) between about 44% and about 62% after 8 hours;~~
~~(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:~~

wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	(Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

Claim 115 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 112 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 116 (currently amended): A controlled-release ~~Galenical~~ preparation of pharmaceutically acceptable form of diltiazem according to Claim 5 ~~selected from the group consisting of Diltiazem and the pharmaceutically acceptable salts~~

~~thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem~~

~~(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:~~

~~(a) between about 4% and about 8% after 2 hours;~~
~~(b) between about 16% and about 21% after 4 hours;~~
~~(c) between about 44% and about 52% after 8 hours;~~
~~(d) between about 69% and about 76% after 14 hours; and~~
~~(e) and in excess of about 85% after 24 hours;~~

~~and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:~~

~~(a) between about 4% and about 15% after 2 hours;~~
~~(b) between about 16% and about 30% after 4 hours;~~
~~(c) between about 44% and about 62% after 8 hours;~~
~~(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:~~

wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants which permits hydration of the core by gastrointestinal fluids.

Claim 117 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 116 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 118 (currently amended): A controlled-release ~~Galenical~~ preparation of pharmaceutically acceptable form of diltiazem according to Claim 5 ~~selected from Diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem~~

~~(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:~~

~~(a) between about 4% and about 8% after 2 hours;~~

~~(b) between about 16% and about 21% after 4 hours;~~

~~(c) between about 44% and about 52% after 8 hours;~~

~~(d) between about 69% and about 76% after 14 hours; and~~

~~(e) and in excess of about 85% after 24 hours;~~

~~and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:~~

~~(a) between about 4% and about 15% after 2 hours;~~

~~(b) between about 16% and about 30% after 4 hours;~~

~~(c) between about 44% and about 62% after 8 hours;~~

~~(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:~~

wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants which permits hydration of the core by gastrointestinal fluids.

Claim 119 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 118 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claims 120-121 (cancelled)

Claim 122 (currently amended): A controlled-release ~~Galenical~~ preparation of pharmaceutically acceptable form of diltiazem according to Claim 1 ~~selected from the group consisting of Diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours~~

~~(Tmax) after administration of the preparation, the preparation being in a sustained release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:~~ wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants which permits hydration of the core by gastrointestinal fluids.

Claim 123 (original): The preparation of claim 122 wherein the microgranules are in capsule form.

Claim 124 (original): The preparation of claim 122 wherein the microgranules are in tablet form.

Claim 125 (previously amended): The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethyl-cellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

Claim 126 (previously amended): The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	(Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025

(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

Claim 127 (previously amended): The preparation of claim 122 or 124 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of diltiazem during the tablet process, together with suitable excipients and adjuvants.

Claim 128 (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 122, 123 or 124 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 129 (previously presented): The preparation of claim 110 wherein the neutral copolymer is selected from the group consisting of

(i) a water-, acid-, and base-insoluble polymer of a neutral acrylic polymer;

(ii) a neutral acrylic copolymer of ethyl acrylate and methyl methacrylate;

(iii) a neutral copolymer without any functional groups that form water insoluble films; and

the lubricant is selected from the group consisting of: talc, magnesium stearate and a polyethylene glycol derivative and/or the hydrophilic polymer is selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof.

Claim 130 (previously presented): The preparation of claim 116, 118 and 122 wherein the lubricant is selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative.

Claim 131 (previously presented): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 129 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 132 (previously presented): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 130 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 133 (**Previously presented**): The preparation of Claim 1 in capsule form.

Claim 134 (**Previously presented**): The preparation of Claim 1 in tablet form.

Claim 135 (**Previously presented**): The preparation of Claim 2 in capsule form.

Claim 136 (**Previously presented**): The preparation of Claim 2 in tablet form.

REMARKS

Entry of the foregoing amendments pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks which follow, are respectfully requested. As indicated at the recent personal interview with Examiner Kishore, the claims are amended herein to consolidate the claimed subject matter in U.S. Serial No. 09/965,338 and 09/567,451. Essentially, the claims now require as an essential element at least one water insoluble neutral copolymer, and further require that the claimed orally administratable controlled-release diltiazem composition comprise a novel combination of in vitro dissolution and in vivo pharmacokinetic properties which render the subject controlled-release compositions suitable for evening administration. That is to say, the subject claims are directed to chronotherapeutic diltiazem compositions, which based on their in vitro and in vivo properties, afford novel and improved methods for treatment of angina, hypertension and stroke because they are effective in the early morning hours when the risk of adverse cardiac events and stroke are at their most elevated.

At the outset the Examiner is thanked for scheduling the recent personal interview held on February 23, 2005 with Primary Examiner Kishore, Paul Maes, PhD of Biovail Inc., Salim Mammajiwalla, PhD of Biovail Inc., Professor Edith Mathiowitz, PhD of Brown University, and the undersigned.

During the interview, proposed amended claims (formally submitted herein) were presented to Examiner Kirshore as well as a draft affidavit by Dr.

Mathiowitz, and exhibits thereto. The rejections based on EPA 856313 made in the subject application as well as the rejection based on WO 93/00093 made in the parent application, 09/465,338 were discussed in great detail.

It was argued that the prior art does not explicitly or inherently teach or suggest chronotherapeutic diltiazem compositions as claimed possessing the recited combination of in vitro dissolution and in vivo pharmacokinetic properties. Dr. Mathiowitz and Dr. Maes explained that these properties are surprisingly achieved by the use of the water swellable and diffusible coating that comprises a specific combination of constituents including in particular, at least one water insoluble swellable neutral copolymer, and which coating is further comprised in an amount sufficient and effective to yield a once-daily administratable chronotherapeutic diltiazem composition possessing the recited in vitro dissolution and in vivo pharmacokinetic properties. Dr. Mathiowitz and Dr. Maes further noted that based on the enhanced clinical efficacy that is afforded by a composition possessing such properties, Cardizem LA®, which has been approved by the FDA, it is now widely prescribed by physicians.

The attendees of the interview referred' to sections of on the draft declaration in support of the fact and that the prior art does not teach or suggest chronotherapeutic compositions as claimed. For example, it was explained by Dr. Maes that it was surprisingly discovered that the specifically claimed in vitro dissolution profile correlates predictably to formulations possessing the desired recited in vivo pharmacokinetic properties. Dr. Mathiowitz further explained

that in her experience in vitro dissolution properties do not predictably or necessarily correlate to desired in vivo properties. Dr. Maes further explained that based on this surprising discovery, the preparation of other chronotherapeutic diltiazem formulations possessing the claimed properties, can be achieved by the use of other commercially available water insoluble swellable neutral copolymers, *e.g.*, Kollicoat® 'SR 30 D, (a polyvinyl acetate neutral copolymer sold by BASF for use in sustained release coating formulations, protective coatings, and sustained-release matrix formulations).

Upon consideration of the exhibits and draft affidavit, Examiner Kishore further requested that an additional exhibit be submitted providing a side-by-side comparison of the claimed diltiazem formulation vis-à-vis the prior art. This request has been accommodated and the Mathiowitz Affidavit submitted herewith includes Exhibits 10 and 11 which contain such side-by-side comparisons.

It is anticipated that the present amendments which consolidate the subject matter claimed in U.S. Serial No. 09/567,451 and U.S. Serial No. 09/465,338 should together with the Mathiowitz affidavit and exhibits place this case in condition for allowance.

Turning now to the outstanding Office Action, claims 52, 62 and 114 were previously indicated to be allowable.

Claims 1-66, 110, 112-119 and 122-132 stand rejected on double patenting grounds based on the claims of U.S. Serial No. 09/465,338. This obviousness based double patenting rejection is respectfully traversed to the extent it may be applicable based on the present amendments which consolidate the subject matter claimed in this and the '338 patent application. Applicants respectfully submit that the claims of the '338 patent application do not teach or suggest chronotherapeutic compositions possessing the recited novel combination of in vitro and in vivo properties. Withdrawal of the double patenting rejection is therefore respectfully solicited.

Claims 1-51, 53-63, 65-66, 110, 112-113, 115-119 and 122-132 further stand rejected based on the teachings of EP 856,313 (hereinafter "EP '313" or "Geoghegan patent").

This rejection is respectfully traversed for the reasons and evidence of record and newly submitted herein, most particularly the side-by-side comparison of the in vivo and in vitro properties of a chronotherapeutic diltiazem composition according to the claims (Diltiazem LA®) to a diltiazem formulation according to EP '313 (Cardiazem CD®)[1]. These side-by-side comparisons unequivocally establish that the diltiazem formulations claimed herein possess very different properties, both in vitro dissolution and in vivo pharmacokinetic properties and are not suggested by the teachings of EP '313.

[1] A side-by-side comparison of the claimed formulation to a formulation according to Wo'093 (Tiazac®) is also provided but not discussed herein as this reference has not been maintained against the claims herein.

As explained, in much detail at the interview, and substantiated by the Mathiowitz Affidavit and Exhibits thereto, the EP '313 patent does not teach or suggest a chronotherapeutic diltiazem formulation possessing the recited combination of coating constituents which are contained in ratios and coating amounts sufficient and effective to provide a chronotherapeutic composition possessing the novel combination of in vitro dissolution and in vivo pharmacokinetic properties claimed herein.

Most especially, Applicants respectfully maintain that the EP '313 patent does not teach or suggest a diltiazem formulation which includes as an essential element at least one water insoluble, swellable neutral copolymer in their diltiazem formulation. Rather, as explained by Dr. Mathiowitz, and evidenced by Exhibits thereto, the only copolymer taught or suggested by EP '313 comprise charged Eudragit® copolymers. However, as Dr. Mathiowitz explains in her affidavit, the neutral copolymer comprised in the claimed diltiazem formulation does not function equivalently to the charged copolymers disclosed in the prior art. Therefore, absent some explicit teaching or motivation in the EP '313 patent, it would not have been obvious based on the teachings of EP '313, which are entirely limited to charged copolymers to have substituted a neutral copolymer for the charged copolymers disclosed therein. However, the reference is totally silent with respect to the inclusion of a neutral swellable copolymer in the disclosed diltiazem formulations.

Such modification further would not have been anticipated or obvious based on the teachings of EP '313 since the effects of such modification are not suggested by the EP '313 reference nor would they have been anticipated based on the then-existing state of the prior art relating to sustained release drug formulations.

It particularly could not have been anticipated that it would yield sustained release diltiazem formulations as claimed that

(i) provide a C_{max} of diltiazem in the blood at between 10 and 15 hours after oral administration;

(ii) exhibit higher bioavailability when given at night than when given in the morning; and

(iii) are bioequivalent when given in the morning with and without food.

To the contrary, as indicated by Dr. Mathiowitz in paragraph 21 of her affidavit, "the controlled-release diltiazem compositions being claimed by Biovail possess very different and clearly superior in vivo and in vitro characteristics vis-à-vis the prior art diltiazem formulations". Moreover, as Dr. Mathiowitz further states in paragraph 23 of her Affidavit in her opinion, "it is truly unexpected that the subject chronotherapeutic diltiazem compositions possess very different pharmacokinetic properties" [by the inclusion of co-sufficent amounts of a neutral, water swellable copolymer].

Dr. Mathiowitz, a renowned expert in sustained drug delivery system further vigorously disagrees with the Examiner's conclusion that EP '313 would suggest the claimed formulations. Indeed, she states in paragraph 27 of her affidavit that "Both of the cited publications [EP '313 and WO'093] are completely silent with respect to a chronotherapeutic composition possessing such properties or the need and intrinsic advantages of a diltiazem formulation possessing such properties [in vivo and in vitro properties of the claimed diltiazem formulations]".

Still further, she states in paragraph 28 of her affidavit that "it could not have been reasonably anticipated that the incorporation of a sufficient amount of a coating layer comprising at least one water insoluble swellable neutral copolymer" . . . "would have resulted in a chronotherapeutic diltiazem formulation possessing the novel and superior pharmacokinetic properties of the subject chronotherapeutic diltiazem formations".

In support of her opinion, Dr. Mathiowitz attests to the fact that "in vitro dissolution properties for a particular drug formulation do not necessarily or predictably correlate to desired in vivo pharmacokinetic properties" and that the design of a formulation possessing desired in vivo properties generally require the variation of many parameters and much experimentation.

Based thereon, and further for the reasons of record, Applicants respectfully submit that the claims patentably distinguish the prior art diltiazem

formulations. With respect to such arguments, Applicants further note the comparative composition Cardiazem LA® is commensurate in scope and corresponds to all of the claims of the present invention.

Applicants further note that the Examiner previously considered similar in vivo and in vitro comparative data, but found it to be unpersuasive to overcome the rejection based on EP '313. Based on Applicants' reading of the final rejection, the Examiner seemed to have two concerns:

(iv) she questioned whether the provided comparison corresponded to all of the claims of the subject application, *e.g.*, based on the number of different independent claims, and

(v) She maintained that the EP '313 patent provided a "generic" teaching with respect to copolymer, and maintained that it would suggest the use of neutral copolymer in lieu of charged copolymers.

These concerns are addressed below. With respect to the former concern, Applicants note that the subject application has been amended to contain a single independent claim (in order to alleviate the Examiner's concern). Additionally, the Mathiowitz Affidavit expressly notes that she has reviewed the constituents and properties of the comparative composition according to the invention (Cardiazem LA®), and compared these constituents and properties to the claims at issue, and is of the opinion that this composition is representative

of all the pending claims. Accordingly, the issue raised by the Examiner as to the comparison not being "commensurate" with the claims should be moot.

With respect to the latter issue, Applicants respectfully maintain that the EP '313 does not provide a "generic" teaching that would suggest the substitution of the charged Eudragit copolymers disclosed in EP '313 with an uncharged (neutral) swellable copolymer.

To the contrary, the only water insoluble swellable copolymer mentioned in EP '313 comprise the charged Eudragit copolymers listed in Exhibit 13 of the Mathiowitz Affidavit. There is absolutely no mention of any neutral copolymers. Nor is there any suggestion in the reference with respect to obtaining diltiazem formulations having the claimed in vivo pharmacokinetic properties, *i.e.,* one that upon evening administration yields peak blood serum levels between 10 and 15 hours after administration.

With respect thereto, the Examiner seemed to suggest in the most recent Office Action that such modification (use of neutral copolymers) and the results achieved thereby (chronotherapeutic composition) would have been of a routine nature. However, this conclusion is far from the truth. To the contrary, as Dr. Mathiowitz explains in her Affidavit the effects of substituting the charged Eudragit copolymer in EP '313 with a neutral copolymer were not obvious but rather were unexpected. She explains that it could not have been predicted how

such modification would have affected the in vitro release or the in vivo pharmacokinetic properties of the resultant sustained release composition.

Rather, as explained by Dr. Mathiowitz, such modification and the effects thereof would not have been obvious since the design of sustained drug release compositions is highly complex and unpredictable and typically involves the variation of many different parameters, and trial and error experimentation, in order to achieve desired in vivo properties. Based on this unpredictability and complexity, it would not have been obvious to have made the proposed copolymer modification, since there would have been no reason to expect that it would afford enhanced results. Indeed, this discovery is the very crux of Applicants' invention.

Also, as explained by Dr. Mathiowitz, the substitution of a charged copolymer with a neutral copolymer would not have been obvious because they are not functionally equivalent. Based thereon, and absent any express or implicit teaching in the reference, there would no reason to substitute a charged copolymer with a neutral copolymer since it would be unknown how such change would affect (potentially adversely impact) the properties of the resultant sustained release composition. Further, it could not have been anticipated that the inclusion of a requisite amount of a water insoluble swellable copolymer in the coating layer would have had such a dramatic effect on in vivo pharmacokinetic properties. Rather, this outcome is only obvious in the benefit of hindsight.

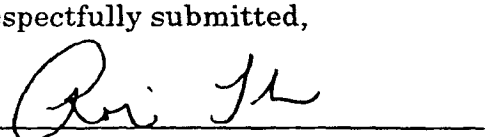
Therefore, absent any suggestion or reason to believe that the incorporation of effective amount of a coating layer containing a water-insoluble swellable neutral copolymer as claimed would have yielded a chronotherapeutic diltiazem formulations possessing the recited novel combination of in vitro and in vivo properties; Applicants respectfully submit that the outstanding prior art rejection should be vacated and this application passed to issue.

If any issues remain after consideration of this Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #100338.55781US).

Respectfully submitted,

April 11, 2005



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